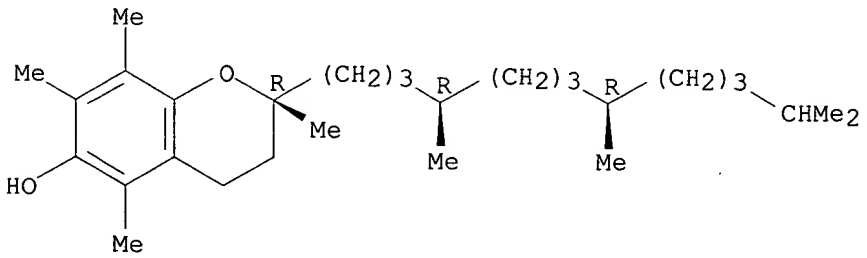
L22 ANSWER 1 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:483860 CAPLUS
DOCUMENT NUMBER: 135:255479
TITLE: Low-density lipoprotein (**LDL**) behavior after in vitro **oxidation** in three groups of diabetics
AUTHOR(S): Seghrouchni, I.; Drai, J.; Bannier, E.; Garcia, I.; Revol, A.
CORPORATE SOURCE: UF Lipides-Glucides, Laboratoire de Biochimie, Centre Hospitalier Lyon Sud, Pierre-Benite, 69495, Fr.
SOURCE: Farmaco (2001), 56(5-6-7), 471-474
CODEN: FRMCE8; ISSN: 0014-827X
PUBLISHER: Elsevier Science S.A.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Diabetes is assocd. with increased morbidity and mortality resulting from cardiovascular disease. It has been established that oxidized LDLs are involved in the genesis of **atherosclerosis**. We have studied **LDL** oxidizability in three types of diabetics: insulin-dependent diabetes mellitus (IDDM), non-insulin-dependent diabetes mellitus (NIDDM) and insulin-**treated** diabetes mellitus type 2 (ITDM2) and a control group. LDLs have been isolated using ultracentrifugation and oxidized by addn. of cupric chloride. With the oxidn. kinetic, we calcd. the lag time and the oxidn. rate. Total fatty acids, .alpha.-tocopherol, and malondialdehyde (MDA) have been measured in native and oxidized LDLs. Oxidized LDLs of diabetics show an important decrease of their polyunsatd. fatty acids with an increase of MDA compared to the control. Diabetics have a significantly lower lag time and a lower level of .alpha.-tocopherol. Our study demonstrates a higher susceptibility to oxidn. of **LDL** from diabetics; this can be explained by alteration in **LDL** compn. or by the **oxidative** process occurring in this disease.

IT **59-02-9**, .alpha.-Tocopherol
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(**LDL** oxidn. assocd. with decreased level of unsatd. fatty acids and .alpha.-tocopherol in **human** with diabetes mellitus)
RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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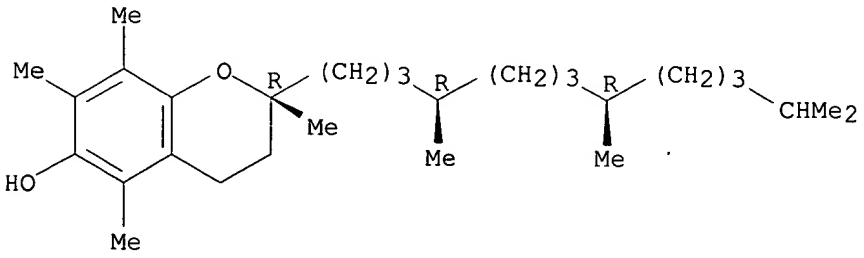
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 2 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:310175 CAPLUS
TITLE: .alpha.-Tocopherol decreases CD36 expression in **human** monocyte-derived macrophages
AUTHOR(S): Devaraj, S.; Hugou, I.; Jialal, I.
CORPORATE SOURCE: Division of Clinical Biochemistry and Human Metabolism, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA
SOURCE: J. Lipid Res. (2001), 42(4), 521-527
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cholesterol-laden macrophages are the hallmark of atherogenesis. The class B scavenger receptor, CD36, binds oxidized low-d. lipoprotein (OxLDL), is found in **atherosclerotic** lesions, and is upregulated by OxLDL. The effects of .alpha.-tocopherol (AT) enrichment of monocyte-derived macrophages on CD36 expression and cholesteryl ester accumulation were examd. using monocytes isolated from normal humans and cultured into macrophages. The macrophages were enriched overnight with AT (25, 50, and 100 .mu.M in medium). **LDL** from normal humans was oxidized or acetylated (AcLDL) and incubated with macrophages for 48 h at 50 or 100 .mu.g AT/mL. The CD36 expression was assessed by flow cytometry. Quant. anal. of scavenger receptor class A (SR-A) activity was performed with 1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanide perchlorate (DiI)-labeled **LDL**. The CD36 expression was maximal after 8-10 days of culture. AT at .gtoreq.50 .mu.M decreased the CD36 expression upregulated by OxLDL and AcLDL. Other **antioxidants** (.beta.- or .gamma.-tocopherol) or protein kinase C inhibitors failed to decrease the CD36 expression. The DiI-AcLDL and DiI-OxLDL uptake was decreased after the AT **treatment**. The cholesteryl ester accumulation was decreased by AT enrichment (77% inhibition in AcLDL + AT, 42% inhibition in OxLDL + AT). Thus, AT decreases both CD36 and SR-A expression and cholesteryl ester accumulation in **human** macrophages. This suggests antiatherogenic properties of AT.

IT **59-02-9**, .alpha. tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(CD36 and scavenger receptor A expression decrease by .alpha.-tocopherol in **human** monocyte-derived macrophages in vitro)
RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE(S): (1) Asmis, R; Eur J Biochem 1995, V233, P171 CAPLUS
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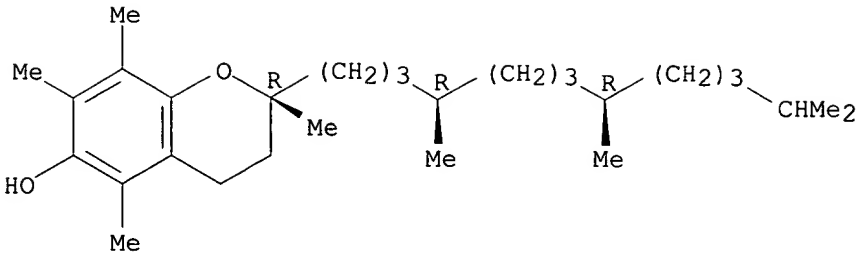
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 3 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:789974 CAPLUS
DOCUMENT NUMBER: 134:321092
TITLE: Oxidized **LDL** upregulates angiotensin II type 1 receptor expression in cultured **human** coronary artery endothelial cells: The potential role of transcription factor NF-.kappa.B
AUTHOR(S): Li, Dayuan; Saldeen, Tom; Romeo, Francesco; Mehta, Jawahar L.
CORPORATE SOURCE: Departments of Medicine and Physiology, University of Arkansas and VA Medical Center, Little Rock, AR, 72205-7199, USA
SOURCE: Circulation (2000), 102(16), 1970-1976
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We demonstrated earlier that angiotensin II (Ang II), by AT1 receptor activation, upregulates oxidized **LDL** (ox-**LDL**) endothelial receptor LOX-1 gene expression and uptake of ox-**LDL** in **human** coronary artery endothelial cells (HCAECs). In this study, we investigated the regulation of Ang II receptors (AT1R and AT2R) by ox-**LDL** and the role of the redox-sensitive transcription factor NF-.kappa.B in this process. HCAECs were incubated with ox-**LDL** for 24 h. Ox-**LDL** (10 to 40 .mu.g protein/mL) upregulated AT1R but not AT2R, mRNA, or protein. Ox-**LDL** degraded I.kappa.B.alpha. in cytoplasm and activated transcription factor NF-.kappa.B (P65) in HCAEC nuclear ext. **Treatment** of cells with the **antioxidant** .alpha.-tocopherol (10 to 50 .mu.mol/L) attenuated ox-**LDL**-mediated degrdn. of I.kappa.B.alpha. and activation of NF-.kappa.B (P65) and inhibited the upregulation of AT1R mRNA and protein. The role of NF-.kappa.B signal transduction was further examd. by use of an NF-.kappa.B inhibitor, caffeic acid phenethyl ester (CAPE). Pretreatment of cells with CAPE inhibited ox-**LDL** -mediated degrdn. of I.kappa.B.alpha. and NF-.kappa.B activation and inhibited ox-**LDL**-induced upregulation of AT1R expression. Incubation of cells with both ox-**LDL** and Ang II increased cell injury, measured as cell viability and LDH release, compared with either ox-**LDL** or Ang II alone. .alpha.-Tocopherol as well as the specific AT1R blocker CV11974 (candesartan) attenuated the cell-injurious effects of ox-**LDL**. These observations suggest an important role of ox-**LDL**-mediated AT1R upregulation in cell injury. In this process, NF-.kappa.B activation seems to play a crit. role in signal transduction. These findings provide a basis for the use of **antioxidants** and AT1R blockers in designing therapy of **atherosclerosis**.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oxidized **LDL** upregulates AT1 receptor expression in cultured **human** coronary artery endothelial cells)
RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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(6) Dimmeler, S; Circ Res 1997, V81, P970 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 4 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:709157 CAPLUS
DOCUMENT NUMBER: 134:85444
TITLE: Vitamin E supplementation of **human** macrophages **prevents** neither foam cell formation nor increased susceptibility of foam cells to lysis by oxidized **LDL**
AUTHOR(S): Asmis, Reto; Jelk, Jennifer
CORPORATE SOURCE: Institute of Biochemistry, University of Basel, Basel, Switz.
SOURCE: Arterioscler., Thromb., Vasc. Biol. (2000), 20(9), 2078-2086
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several studies in macrophage cell lines, rodent macrophages, and animal models of **atherosclerosis** suggest that vitamin E may **prevent** the formation of foam cells. We tested this hypothesis in a fully autologous in vitro model of **human** foam cell formation with or without added RRR-.alpha.-tocopherol. Macrophages continuously increased their .alpha.-tocopherol/total cholesterol ratio during maturation, demonstrating that these cells accumulate .alpha.-tocopherol at an even higher rate than cholesterol. In the presence of nonsupplemented serum, we obsd. no correlation between serum vitamin E levels and the increase in the cellular .alpha.-tocopherol/total cholesterol ratio. Under supplemented conditions, a 3.1-fold increase in the mean serum .alpha.-tocopherol/total cholesterol ratio resulted in a corresponding mean 3.5-fold increase in the cellular .alpha.-tocopherol/total cholesterol ratio. Vitamin E loading had no effect on the lipid compn. of macrophages and did not affect their growth. Foam cell formation was stimulated in mature nonsupplemented and vitamin E-loaded macrophages for 1 wk with 50 .mu.g autologous aggregated low-d. lipoprotein (**LDL**) in the presence of nonsupplemented and vitamin E-loaded serum, resp. We obsd. no effect of vitamin E supplementation on the formation of foam cells. The foam cell formation resulted in 36 and 44% decreases in the cellular .alpha.-tocopherol/total cholesterol ratio in nonsupplemented and vitamin E-supplemented foam cells, resp. The loss of vitamin E was accelerated with increasing concns. of aggregated **LDL** and was accompanied by increased susceptibility of these foam cells to succumb to the cell lytic effects of oxidized **LDL** (OxLDL). Vitamin E supplementation did not protect the macrophages or foam cells from OxLDL-mediated cell lysis, suggesting that vitamin E loss in foam cells is not the cause of their increased susceptibility to lysis.

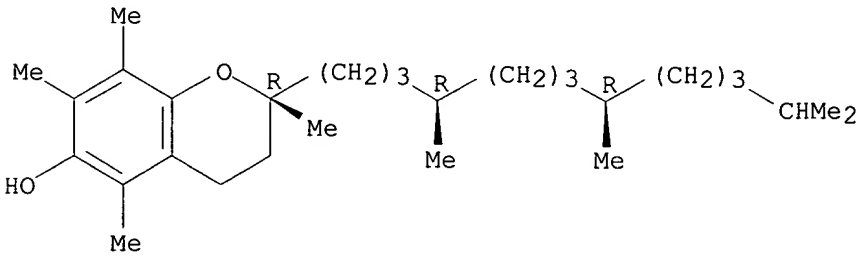
The beneficial effects of vitamin E in cardiovascular disease obsd. in humans are due neither to decreased propensity of macrophages to form foam cells nor increased resistance of these cells to cytolytic OxLDL.

IT **59-02-9**, .alpha. Tocopherol
RL: BPR (Biological process); FFD (Food or feed use); BIOL (Biological study); PROC (Process); USES (Uses)
(vitamin E supplement in **human** macrophage cultures does not **prevent** foam cell formation or increased susceptibility of foam cells to lysis by oxidized low-d. lipoproteins)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 5 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:598525 CAPLUS

DOCUMENT NUMBER: 134:98916

TITLE: Remnant lipoproteins induce proatherothrombogenic molecules in endothelial cells through a redox-sensitive mechanism

AUTHOR(S): Doi, Hideki; Kagiyama, Kiyotaka; Oka, Hideki; Sugiyama, Seigo; Ogata, Nobuhiko; Koide, Shun-Ichi; Nakamura, Shin-Ichi; Yasue, Hirofumi

CORPORATE SOURCE: Department of Cardiovascular Medicine, Kumamoto University School of Medicine, Kumamoto City, 860-8556, Japan

SOURCE: Circulation (2000), 102(6), 670-676
CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background - Triglyceride-rich lipoproteins (TGLs) are atherogenic. However, their cellular mechanisms remain largely unexplained. This study examd. the effects of isolated remnant-like lipoprotein particles (RLPs) on the expression of intercellular adhesion mol.-1 (ICAM-1), vascular cell adhesion mol.-1 (VCAM-1), and tissue factor (TF), proatherothrombogenic mols., in cultured **human** endothelial cells. Methods and Results - RLPs were isolated from plasma of hypertriglyceridemic patients by use of the immunoaffinity gel mixt. of anti-apoA-1 and anti-apoB-100 monoclonal antibodies. The incubation of cells with RLPs significantly upregulated mRNA and protein expression of these mols. Total TGLs (d<1.006) and **LDL** had fewer or minimal effects on expression of these mols. compared with RLPs. RLPs increased intracellular

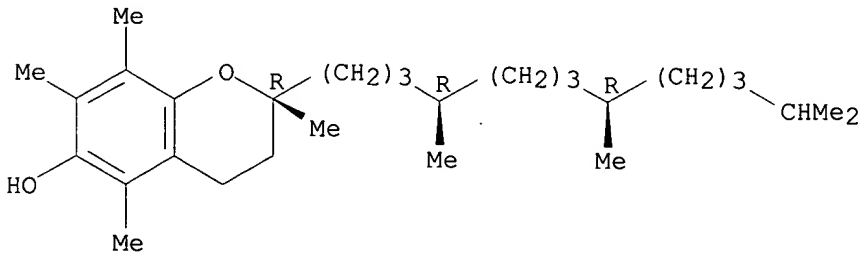
oxidant levels, as assessed with an **oxidant**-sensitive probe. Combined incubation with .alpha.-tocopherol or N-acetylcysteine, both **antioxidants**, suppressed RLP-induced increase in expression of these mols. In patients with higher plasma levels of RLPs, plasma levels of sol. forms of ICAM-1 and VCAM-1 were significantly higher than in patients with lower RLP levels. **Treatment** with .alpha.-tocopherol for 1 mo decreased levels of the sol. adhesion mols. concomitantly with an increase in resistance of RLPs to **oxidative** modification in patients with high RLP levels. Conclusions - RLPs upregulated endothelial expression of ICAM-1, VCAM-1, and TF, proatherothrombogenic mols., partly through a redox-sensitive mechanism. RLPs may have an important role in atherothrombotic complications in hypertriglyceridemic patients.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(remnant lipoproteins from hypertriglyceridemics upregulated endothelial expression of proatherothrombogenic ICAM-1, VCAM-1, and tissue factor in **human** endothelial cells through redox-sensitive mechanism in relation to)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 6 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:445923 CAPLUS
DOCUMENT NUMBER: 133:163662
TITLE: Inhibitory effect of flavonoids on low-density lipoprotein **peroxidation** catalyzed by mammalian 15-lipoxygenase
AUTHOR(S): Da Silva, Edson Luiz; Abdalla, D. S. P.; Terao, J.
CORPORATE SOURCE: Department of Clinical Analysis, Health Sciences Center, Federal University of Santa Catarina, Florianopolis, SC, 88040-970, Brazil
SOURCE: IUBMB Life (2000), 49(4), 289-295
CODEN: IULIF8; ISSN: 1521-6543
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lipoxygenase-dependent low-d. lipoprotein (**LDL**) oxidn. may be involved in atherogenesis. Inhibition of lipoxygenase-induced lipid peroxidn. may be an important mode to suppress the development of

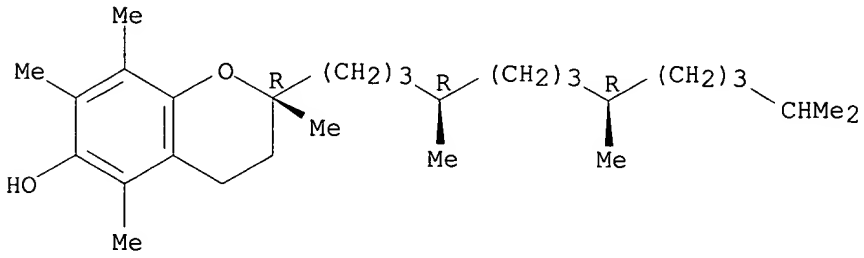
atherosclerosis. Because dietary **antioxidants** inhibit **LDL** oxidn. in vitro and their intake is inversely assocd. with coronary heart diseases, we compared the inhibitory effects of 3 typical flavonoids (quercetin, epicatechin, flavone) with the effects of .alpha.-tocopherol and ascorbic acid against **human LDL** oxidn. catalyzed by mammalian (rabbit) 15-lipoxygenase in vitro. The **oxidative** modification of **LDL** was monitored by measurement of cholesteryl ester hydroperoxide (CE-OOH) formation and consumption of **antioxidants** by HLPC. Quercetin and epicatechin were the strongest inhibitors of **LDL** oxidn. catalyzed by 15-lipoxygenase; ascorbic acid was an effective inhibitor in the first 3 h of oxidn.; 5-fold .alpha.-tocopherol-enriched **LDL** showed partial inhibition of CE-OOH formation only after 4-6 h of incubation. Flavone had no effect. Quercetin, ascorbic acid, and .alpha.-tocopherol were consumed in the first 3 h of incubation. Consumption of **LDL** .alpha.-tocopherol was partially inhibited by ascorbic acid and quercetin, whereas epicatechin and flavone were without effect. The results emphasize the inhibitory effects of the dietary flavonoids quercetin and epicatechin on 15-lipoxygenase-mediated **LDL** lipid peroxidn. At similar concns., they are stronger **antioxidants** than ascorbic acid, .alpha.-tocopherol, and flavone.

IT **59-02-9**, .alpha. Tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(dietary flavonoids inhibitory effects on **human** low-d. lipoprotein peroxidn. catalyzed by rabbit 15-lipoxygenase in vitro)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 7 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:358264 CAPLUS

DOCUMENT NUMBER: 133:103130

TITLE: Modulation of base excision repair by low density lipoprotein, oxidized low density lipoprotein and **antioxidants** in mouse monocytes

AUTHOR(S): Chen, Kuang-Hua; Srivastava, Deepak K.; Singhal, Rakesh K.; Jacob, Sam; Ahmed, Ahmed E.; Wilson, Samuel

H.

CORPORATE SOURCE: Sealy Center for Molecular Science, University of Texas Medical Branch, Galveston, TX, 77555, USA

SOURCE: Carcinogenesis (2000), 21(5), 1017-1022
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

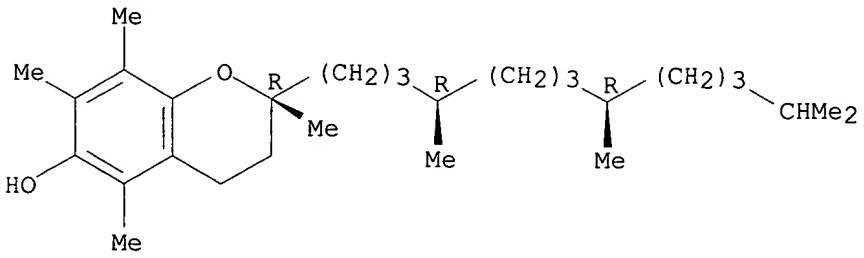
AB In the present study, we found that oxidized low d. lipoprotein, but not low d. lipoprotein, down-regulated base excision repair activity in exts. of mouse monocyte cell line PU5-1.8. An enzyme required in this pathway, DNA polymerase .beta., was also down-regulated. In contrast, **treatment** of monocytes with a combination of ascorbate and .alpha.-tocopherol up-regulated base excision repair activity and expression of DNA polymerase .beta.. Co-**treatment** of monocytes with **antioxidants** plus oxidized low d. lipoprotein **prevented** down-regulation by oxidized low d. lipoprotein. **Oxidative** DNA damage, as measured by 8-hydroxyguanine accumulation in genomic DNA, was found in cells **treated** with oxidized low d. lipoprotein; 8-hydroxyguanine was not found in the cells **treated** with low d. lipoprotein, **antioxidants** or oxidized low d. lipoprotein plus **antioxidants**. These results establish a linkage between the DNA base excision repair pathway, **oxidative** DNA damage and oxidized low d. lipoprotein **treatment** in mouse monocytes. Since oxidized low d. lipoprotein is implicated in chronic disease conditions such as atherogenesis, these findings facilitate understanding of genetic toxicol. mechanisms related to **human** health and disease.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(modulation of base excision repair by low d. lipoprotein, oxidized low d. lipoprotein and **antioxidants** in mouse monocytes)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 8 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:569296 CAPLUS

DOCUMENT NUMBER: 131:346455

TITLE: Lack of **antioxidant** activity of the antiatherogenic compound l-arginine

AUTHOR(S): Adams, M. R.; Phu, C. V.; Stocker, R.; Celermajer, D. S.

CORPORATE SOURCE: Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia

SOURCE: Atherosclerosis (Shannon, Irel.) (1999), 146(2), 329-335
CODEN: ATHSBL; ISSN: 0021-9150

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

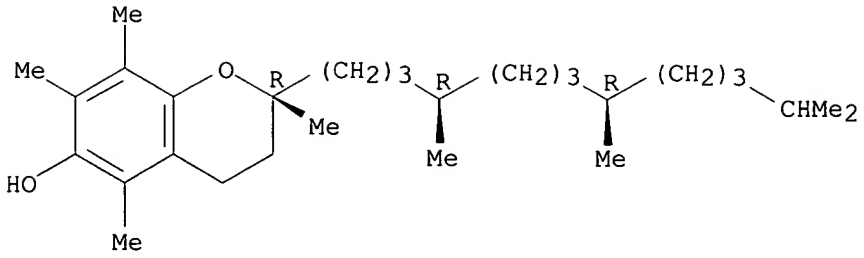
AB L-Arginine, the physiol. substrate of nitric oxide synthase, has antiatherogenic properties in animal models of **atherosclerosis**, and improves endothelial function in hypercholesterolemic humans. Some of these effects may be mediated by increased prodn. of nitric oxide; however, some investigators have postulated a direct **antioxidant** action related to its aminoguanidine moiety. We aimed therefore was to assess the **antioxidant** properties of l-arginine. The **antioxidant** properties of 200 .mu.M l-arginine, 200 .mu.M d-arginine and 200 .mu.M l-glutamate were compared with the powerful **antioxidant** ascorbate and a control (phosphate-buffered saline). Compds. were tested using four in vitro methods: (1) the Esterbauer technique (which tests the ability of the compds. to scavenge free radicals or chelate transition metals); (2) the effect on the autoxidn. of ascorbate; (3) anti-tocopherol mediated peroxidn. (which tests the compd.'s ability to synergize with .alpha.-tocopherol to **prevent** mild chem. induced **LDL** oxidn.); and (4) the ability of the compds. to attenuate .alpha.-tocopherol radical in micellar emulsions (TRAA). The above methods were repeated using the metabolites of the test compds. after incubation with **human** endothelial cells. Ex vivo studies were then carried out by measuring levels of lipid peroxide prodn. (using HPLC with UV and chemiluminescence detection) in three healthy volunteers before and 2 h after a single 7-g oral dose of l-arginine. By the Esterbauer technique, l-arginine increased lag time by 45% compared to control, as did d-arginine by 50%; l-glutamate had no effect and ascorbate increased lag time by 325%. Neither l-arginine, d-arginine or l-glutamate had significant effects on the autoxidn. of ascorbate or anti-tocopherol mediated peroxidn. By the TRAA method, l-arginine had a small effect on **preventing** the decay of tocopherol. The results were similar for the studies of the compd.'s metabolites. In ex vivo studies, no changes were seen in lipid peroxide levels following acute dosage with l-arginine. L-Arginine has only weak and non-specific **antioxidant** effects, suggesting that its major cardioprotective benefits occur through other mechanisms, such as via the nitric oxide pathway.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antioxidant** activity lack of antiatherogenic compd. L-arginine)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 38
REFERENCE(S):
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(2) Adams, M; Circulation 1997, V95, P662 CAPLUS
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(4) Adams, M; J Am Coll Cardiol 1997, V29, P491 CAPLUS
(8) Boger, R; Circulation 1997, V96, P1282 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 9 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:456810 CAPLUS
DOCUMENT NUMBER: 131:227002
TITLE: Secondary radicals derived from chloramines of apolipoprotein B-100 contribute to HOCl-induced lipid **peroxidation** of low-density lipoproteins
AUTHOR(S): Hazell, Linda J.; Davies, Michael J.; Stocker, Roland
CORPORATE SOURCE: Biochemistry Group, The Heart Research Institute, Camperdown, 2050, Australia
SOURCE: Biochem. J. (1999), 339(3), 489-495
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oxidn. of low-d. lipoproteins (**LDL**) is thought to contribute to atherogenesis. Although there is increasing evidence for a role of **myeloperoxidase**-derived **oxidants** such as hypochlorite (HOCl), the mechanism by which HOCl modifies **LDL** remains controversial. Some studies report the protein component to be the major site of attack, whereas others describe extensive lipid peroxidn. The present study addresses this controversy. The results obtained are consistent with the hypothesis that radical-induced oxidn. of **LDL** 's lipids by HOCl is a secondary reaction, with most HOCl consumed via rapid, non-radical reaction with apolipoprotein B-100. Subsequent incubation of HOCl-**treated LDL** gives rise to lipid peroxidn. and **antioxidant** consumption in a time-dependent manner. Similarly, with **myeloperoxidase**/H2O2/Cl- (the source of HOCl in vivo), protein oxidn. is rapid and followed by an extended period of lipid peroxidn. during which further protein oxidn. does not occur. The secondary lipid peroxidn. process involves EPR-detectable radicals, is attenuated by a radical trap or **treatment** of HOCl-oxidized **LDL** with methionine, and occurs less rapidly when the lipoprotein was depleted of .alpha.-tocopherol. The initial reaction of low concns. of HOCl (400-fold or 800-fold molar excess) with **LDL** therefore seems to occur primarily by two-electron reactions with side-chain sites on apolipoprotein B-100. Some of the initial reaction products, identified as lysine-residue-derived chloramines, subsequently undergo homolytic (one-electron) reactions to give radicals that initiate **antioxidant** consumption and lipid oxidn. via tocopherol-mediated peroxidn. The identification of these chloramines, and the radicals derived from them, as initiating agents in **LDL** lipid peroxidn. offers potential new targets for **antioxidative** therapy in atherogenesis.

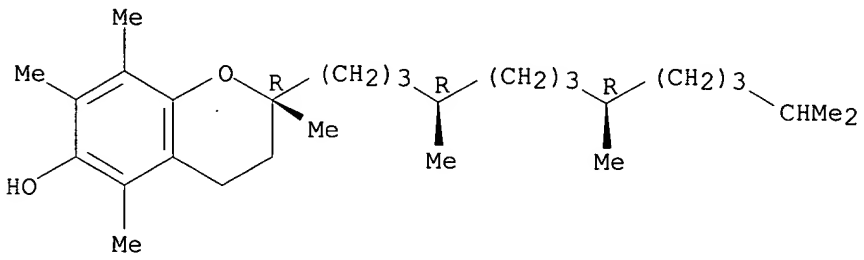
IT **59-02-9**, .alpha.-Tocopherol

RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(-mediated lipid peroxidn.; secondary radicals derived from lysine-residue-derived chloramines of **human** apolipoprotein B-100 contribute to HOCl-induced lipid peroxidn. of low-d. lipoproteins in relation to atherogenesis and)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 47

REFERENCE(S):
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(2) Bandara, B; J Org Chem 1994, V59, P1642 CAPLUS
(3) Berliner, J; Free Radicals Biol Med 1996, V20, P707 CAPLUS
(4) Bernofsky, C; Free Radicals Res Commun 1990, V9, P303 CAPLUS
(5) Bohlen, P; Arch Biochem Biophys 1973, V155, P213 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 10 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:429534 CAPLUS

DOCUMENT NUMBER: 131:182962

TITLE: A role for reduced coenzyme Q in **atherosclerosis**?

AUTHOR(S): Thomas, Shane R.; Witting, Paul K.; Stocker, Roland

CORPORATE SOURCE: The Biochemistry Group, The Heart Research Institute, Camperdown, 2050, Australia

SOURCE: BioFactors (1999), 9(2-4), 207-224
CODEN: BIFAEU; ISSN: 0951-6433

PUBLISHER: IOS Press

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review, with 119 refs. Substantial evidence implicates **oxidative** modification of low d. lipoprotein (**LDL**) as an important event contributing to atherogenesis. As a result, the elucidation of the mol. mechanisms by which **LDL** is oxidized and how such oxidn. is **prevented** by **antioxidants** has been a significant research focus. Studies on the antioxidn. of **LDL** lipids have focused primarily on .alpha.-tocopherol (.alpha.-TOH), biol. and chem. the most active form of vitamin E and quant. the major lipid-sol. **antioxidant** in exts. prepd. from **human** **LDL**. In addn. to .alpha.-TOH, plasma **LDL** also contains low levels of ubiquinol-10 (CoQ10H2; the reduced form of coenzyme Q10). Recent studies have shown that in oxidizing plasma lipoproteins .alpha.-TOH can exhibit anti- or pro-**oxidant** activities for the lipoprotein's lipids exposed to a vast array of **oxidants**. This article reviews the mol. action of .alpha.-TOH in **LDL** undergoing "mild" radical-initiated lipid peroxidn., and discusses how small levels

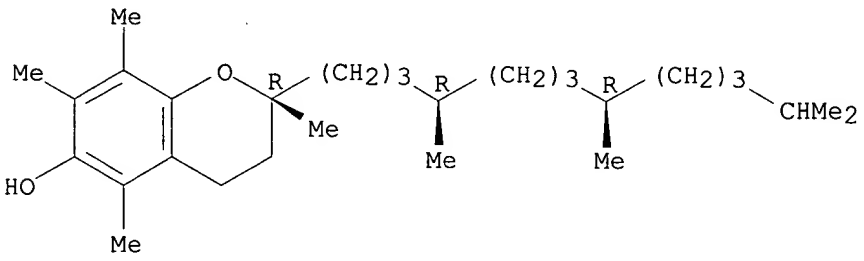
of CoQ10H2 can represent an efficient **antioxidant** defense for lipoprotein lipids. We also comment on the levels .alpha.-TOH, CoQ10H2 and lipid oxidn. products in the intima of patients with coronary artery disease and report on preliminary studies examg. the effect of coenzyme Q10 supplementation on atherogenesis in apolipoprotein E knockout mice.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(.alpha.-tocopherol, coenzyme Q and **LDL** oxidn. in **atherosclerosis**)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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(4) Berliner, J; Free Radic Biol Med 1996, V20, P707 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 11 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:275723 CAPLUS

DOCUMENT NUMBER: 131:68100

TITLE: Protection of low density lipoprotein **oxidation** by the **antioxidant** agent IRFI005, a new synthetic hydrophilic vitamin E analogue

AUTHOR(S): Iuliano, Luigi; Pedersen, Jens Z.; Camastra, Caterina; Bello, Valentina; Ceccarelli, Stefano; Violi, Francesco

CORPORATE SOURCE: Institute of Clinical Medicine I, University La Sapienza, Rome, 00185, Italy

SOURCE: Free Radical Biol. Med. (1999), 26(7/8), 858-868
CODEN: FRBMEH; ISSN: 0891-5849

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

Pull these refs

AB The **oxidative** modification of low d. lipoprotein (**LDL**) is thought to be an important factor in the initiation and development of **atherosclerosis**. **Antioxidants** have been shown to protect **LDL** from oxidn. and to inhibit **atherosclerosis** development in animals. Potent synthetic **antioxidants** are currently being tested, but they are not necessarily safe for **human** use. We here characterize the **antioxidant** activity of IRFI005, the active metabolite of Raxofelast (IRFI0016) that is a novel synthetic analog of vitamin E under clin. development, and

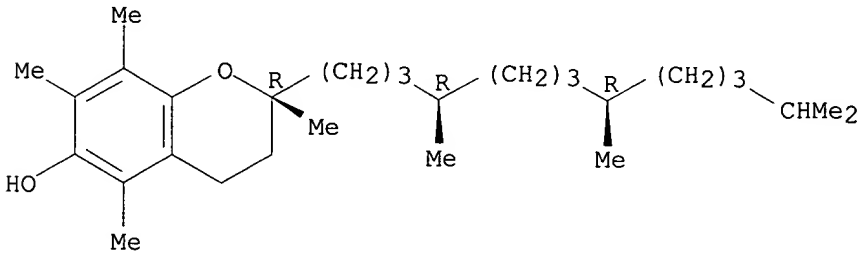
demonstrate that it **prevents oxidative** modification of **LDL**. IFI005 inhibited the **oxidative** modification of **LDL**, measured through the generation of MDA, electrophoretic mobility and apo B100 fluorescence. During the oxidn. process IRFI005 was consumed with the formation of the benzoquinone oxidn. product. The powerful **antioxidant** activity of IRFI005 is at least in part mediated by a chain breaking mechanism as it is an efficient peroxyl radical scavenger with a rate const. k(IRFI005 + LOO.degree.) of 1.8 .times. 106 M-1s-1.4. IRFI005 substantially preserved **LDL** -assocd. **antioxidants**, .alpha.-tocopherol and carotenoids, and when co-incubated with physiol. levels of ascorbate provoked a synergistic inhibition of **LDL** oxidn. Also the co-incubation of IRFI005 with Trolox caused a synergistic effect, and a lag phase in the formation of the trolox-benzoquinone oxidn. product. A synergistic inhibition of lipid peroxidn. was also demonstrated by co-incubating IRFI005 and .alpha.-tocopherol incorporated in linoleic acid micelles. These data strongly suggest that IRFI005 can operate by a recycling mechanism similar to the vitamin E/ascorbate system.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(linoleic acid micelles; **antioxidant** agent IRFI005 protection of **LDL** oxidn. and synergism with .alpha.-tocopherol linoleic acid micelles)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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(5) Boyd, S; J Am Chem Soc 1990, V112, P5724 CAPLUS
(6) Buckley, M; Drugs 1989, V37, P761 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 12 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:190910 CAPLUS
DOCUMENT NUMBER: 130:321001
TITLE: 17.beta.-estradiol reduces tumor necrosis factor-.alpha.-mediated **LDL** accumulation in the artery wall
AUTHOR(S): Walsh, Barbara A.; Mullick, Adam E.; Walzem, Rosemary L.; Rutledge, John C.
CORPORATE SOURCE: Division of Cardiovascular Medicine, Department of Medicine, University of California, Davis, CA, 95616, USA
SOURCE: J. Lipid Res. (1999), 40(3), 387-396
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English

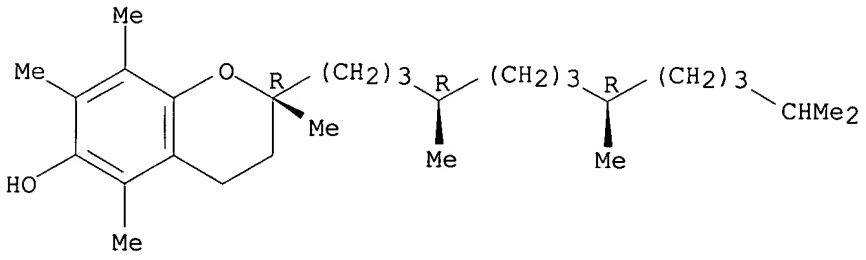
AB Estrogens have direct effects on the vascular wall that may **prevent** the development of **atherosclerosis**. In particular, estrogens, such as 17.beta.-estradiol (estradiol), are known to have potent **antioxidant** activity. Tumor necrosis factor-.alpha. (TNF) is found in **human** atheroma and produces oxygen-derived free radicals. These oxygen-derived free radicals may modify low d. lipoproteins (**LDL**) and increase **LDL** binding in the artery wall. This study examines whether: 1. does TNF increase **LDL** accumulation in the artery wall and 2. can the TNF-mediated increase in **LDL** accumulation be **prevented** by the **antioxidant** activity of estradiol Carotid arteries from ovariectomized 3-mo-old rats were removed and perfused with fluorescently labeled **LDL** and arterial **LDL** flux was measured using quant. fluorescence microscopy. In six arteries, addn. of TNF (10 ng/mL) to the perfusate resulted in a 2.3-fold increase in the rate of **LDL** accumulation (1.50 .+-. 0.37 ng/min per cm2 vs. 3.38 .+-. 0.48 ng/min per cm2; $P < 0.01$). Estradiol (65 pg/mL) and .alpha.-tocopherol (6 mg/L) both attenuated TNF-mediated **LDL** accumulation ($P < 0.05$), indicating that TNF may exert its effects on **LDL** accumulation through cellular prodn. of oxygen-derived free radicals. These results support an **antioxidant** role for estradiol in the protection against **LDL** accumulation in the artery wall and subsequent progression of **atherosclerosis**.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(estradiol reduces tumor necrosis factor-.alpha.-mediated **LDL** accumulation in the artery wall)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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(8) Goldstein, J; Proc Natl Acad Sci USA 1979, V76, P333 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 13 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:172375 CAPLUS
DOCUMENT NUMBER: 130:295991
TITLE: **Antioxidant** property of dietary phenolic agents in a **human LDL-oxidation** ex vivo model: interaction of

protein binding activity

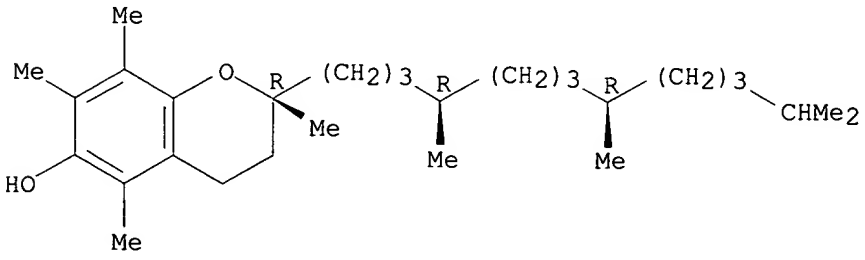
AUTHOR(S): Wang, Weiqun; Goodman, Marc T.
CORPORATE SOURCE: Cancer Research Center, University of Hawaii, Honolulu, HI, 96813, USA
SOURCE: Nutr. Res. (N. Y.) (1999), 19(2), 191-202
CODEN: NTRSDC; ISSN: 0271-5317
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB High consumption of **antioxidant**-rich vegetables and fruits has been assocd. with decreased risk of cardiovascular diseases and cancer. Dietary **antioxidants** may decrease the risk of **atherosclerosis** by inhibiting **oxidative** damage of lipoproteins. Phenolic agents are major dietary **antioxidants** occurring in high concns. in edible plants. We examd. the **antioxidant** properties of 26 common dietary phenolic agents in a **LDL**-oxidn. ex vivo model. Pooled blood plasma from 22 healthy humans was incubated with 20-200 .mu.M of each phenolic agent, **LDL** were then isolated by affinity chromatog. and immediately assessed for **oxidative** susceptibility by measuring Cu-induced formation of conjugated dienes. All phenolic agents tested showed dose-dependent inhibition of **LDL** oxidn., varying between 2 and 110% relative to .alpha.-tocopherol. In addn. to the structural features, the protein binding activity of phenolic agents, as measured with bovine skin proteins as protein matrix, correlated with the **antioxidant** property (r = 0.777). The data not only show the **antioxidant** property of 26 dietary phenolic agents in this ex vivo model, but also indicate possible involvement of phenol-protein interactions in the biol. inhibition of **LDL**-oxidn. Both chem. reducing ability and availability at the site of **LDL** components may be necessary for these major dietary **antioxidants** to **prevent LDL** oxidn. in vivo.

IT **59-02-9**, .alpha. Tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(dietary phenolic **antioxidant** compds. effects on **human LDL**-oxidn. ex vivo and interaction of protein binding activity)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 14 OF 60 CAPLUS COPYRIGHT 2001 ACS

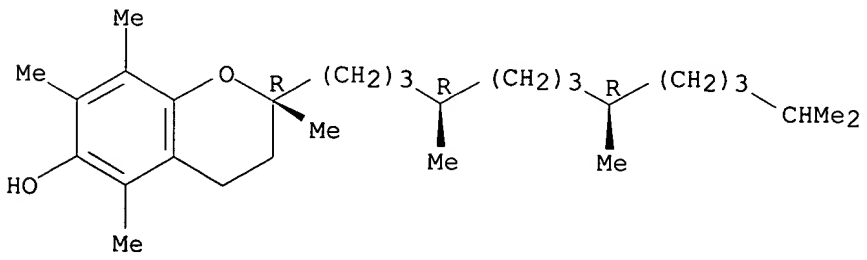
ACCESSION NUMBER: 1998:803794 CAPLUS
DOCUMENT NUMBER: 130:167596
TITLE: .alpha.-tocopherol enrichment of monocytes decreases agonist-induced adhesion to **human** endothelial cells
AUTHOR(S): Islam, Kazi Nazrul; Devaraj, Sridevi; Jialal, Ishwarlal
CORPORATE SOURCE: Departments of Pathology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, 75235-9073, USA
SOURCE: Circulation (1998), 98(21), 2255-2261
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Monocyte-endothelium adhesion is a crucial early event in atherogenesis. Several reports indicate that .alpha.-tocopherol (AT) is a potent **antioxidant** in plasma and **LDL** and also has intracellular effects that are antiatherogenic. Recently, it has been shown that AT supplementation results in decreased monocyte-endothelial cell adhesion. However, there is a paucity of data on the mechanisms by which AT inhibits adhesion of monocytes. We studied the effect of AT enrichment of a **human** monocytic cell line, U937, on adhesion to **human** umbilical vein endothelial cells (HUVECs). Both lipopolysaccharide (LPS)- and N-formyl-methionyl-leucyl-phenylalanine (FMLP)-stimulated U937 adhesion to HUVECs were studied. AT (50 and 100 .mu.mol/L) significantly decreased adhesion of both LPS- and FMLP-stimulated U937 cells to HUVECs (LPS-**treated** cells, $P<0.0125$; FMLP-**treated** cells, $P<0.05$). Expression of the adhesion mols. CD11a, CD11b, CD11c, very late antigen-4 (VLA-4), and L-selectin, as assessed by flow cytometry, was increased in the stimulated U937 cells, and AT resulted in significant redn. in the expression of CD11b and VLA-4. In addn., activation of the transcription factor nuclear factor-.kappa.B (NF-.kappa.B), as assessed by gel shift assays, was inhibited by pretreatment with AT in LPS-**treated** U937 cells. Conclusions-AT significantly decreases adhesion of activated monocytes to endothelial cells by decreasing expression of CD11b and VLA-4 on monocytes, possibly by inhibiting the activation of NF-.kappa.B.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(.alpha.-tocopherol enrichment of monocytes decreases agonist-induced adhesion to **human** endothelial cells)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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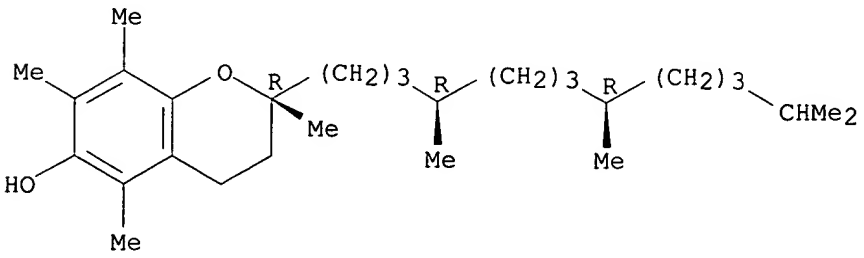
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 15 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:789572 CAPLUS
DOCUMENT NUMBER: 130:138667
TITLE: .alpha.-Tocopherol protects the **peroxidative** modification of **LDL** to be recognized by **LDL** receptors
AUTHOR(S): Sakuma, Nagahiko; Yosikawa, Masae; Hibino, Takeshi; Okada, Masami; Jinno, Yasunari; Tamai, Nozomu; Sasai, Kanna; Yoshimata, Takayuki; Kunimatsu, Mitoshi; Fujinami, Takao
CORPORATE SOURCE: Third Department of Internal Medicine, Nagoya City University, Medical School, Nagoya, 467-8601, Japan
SOURCE: J. Nutr. Sci. Vitaminol. (1998), 44(5), 697-703
CODEN: JNSVA5; ISSN: 0301-4800
PUBLISHER: Center for Academic Publications Japan
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Peroxidatively** modified low-d. lipoprotein (**LDL**) may contribute to the **atherosclerotic** process. Protecting **LDL** against lipid peroxidn. may retard the progression of **atherosclerosis**. The protective effects of .alpha.-tocopherol on Cu-catalyzed **LDL peroxidative** modification were examd. by measurement of the concn. of lipid hydroperoxides in **human** **LDL** and by the uptake of **LDL** cholesterol by **human** lymphocytes via the **LDL** receptor-mediated pathway. The levels of lipid hydroperoxides in **LDL** showed that .alpha.-tocopherol inhibited the **peroxidative** modification of **LDL**. It also preserved the ability of **LDL** to be recognized by **LDL** receptors in peripheral blood lymphocytes to the same extent as native **LDL**. Thus, .alpha.-tocopherol may protect **LDL** against **peroxidative** modification and maintain its ability to act as a ligand for **LDL** receptors in vivo.

IT **59-02-9**, .alpha. Tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(low-d. lipoprotein lipid peroxidn **prevention** by .alpha.-tocopherol and protection of recognition by **LDL** receptors of **human** lymphocytes)
RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 35
REFERENCE(S): (1) Abe, K; Bunseki Kagaku 1984, V33, PE309 CAPLUS
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(3) Boyum, A; Scand J Clin Lab Invest (Suppl) 1968, V21, P77 CAPLUS
(4) Brown, M; Science 1986, V232, P34 CAPLUS
(5) Burton, G; J Am Chem Soc 1980, V102, P7791 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

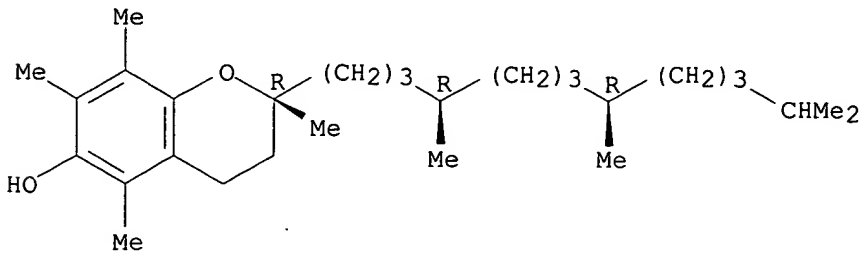
L22 ANSWER 16 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:458052 CAPLUS
DOCUMENT NUMBER: 129:188675
TITLE: Monocyte superoxide production is inversely related to normal content of .alpha.-tocopherol in low-density lipoprotein
AUTHOR(S): Cachia, Odile; Leger, Claude L.; Descomps, Bernard
CORPORATE SOURCE: Laboratoire de Biologie et Biochirnimie des Lipides, Universite de Montpellier, F-34060, Fr.
SOURCE: Atherosclerosis (Shannon, Irel.) (1998), 138(2), 263-269
CODEN: ATHSBL; ISSN: 0021-9150
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

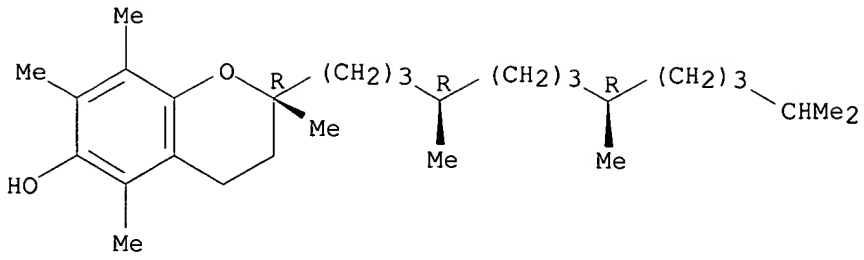
AB Vitamin E (.alpha.-tocopherol) is a potent peroxyl radical scavenger. According to the **oxidative** theory of **atherosclerosis**, it **prevents** oxidn. of low-d. lipoprotein (**LDL**) and thereby lowers the risk of cardiovascular disease. It also mediates cell actions, and specifically decreases monocyte superoxide anion-prodn. (O2.bul.--prodn.), which is involved in **LDL** oxidn. We investigated whether .alpha.-tocopherol-contg. **LDL** decreases this prodn. in a manner dependent on the **LDL** .alpha.-tocopherol content (the .alpha.-tocopherol/apoB molar ratio) in **human**, phorbol ester-stimulated, adherent monocytes. O2.bul.--prodn. was inhibited by native **LDL** (n-**LDL**) in a manner highly sensitive to the increasing .alpha.-tocopherol content (range 4.5-8). In addn.: (1) inhibition was greater when .alpha.-tocopherol was assocd. to acetylated **LDL** (ac-**LDL**), the maximal percentage of inhibition being 80% as opposed to 35% for n-**LDL**; (2) the .alpha.-tocopherol overloading of either form of **LDL** did not produce further inhibition; (3) the free form of .alpha.-tocopherol produced lower inhibition compared with the lipoprotein-assocd. forms; (4) inhibition was not related to the cell content of .alpha.-tocopherol. It is proposed that the cell targeting of .alpha.-tocopherol is crucial to the inhibition of monocyte O2.bul.--prodn., and thus that the role of normal **LDL**-.alpha.-tocopherol contents (range 6-8) in the **prevention** of atherogenic processes needs to be reexamd.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(monocyte superoxide prodn. is inversely related to normal content of .alpha.-tocopherol in low-d. lipoprotein)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



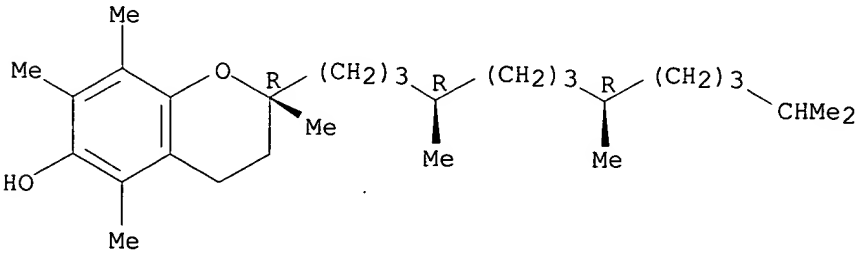


L22 ANSWER 17 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:774806 CAPLUS
DOCUMENT NUMBER: 128:46492
TITLE: .alpha.-Tocopherol, .beta.-carotene, and **oxidative** modification of **human** low-density lipoprotein
AUTHOR(S): Bowen, Hazel T.; Omaye, Stanley T.
CORPORATE SOURCE: Department of Nutrition, University of Nevada, Reno, NV, 89557, USA
SOURCE: Oxid., Antioxid. Free Radicals (1997), 113-123. Editor(s): Baskin, Steven I.; Salem, Harry. Taylor & Francis: Washington, D. C. CODEN: 65KLAO
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review, with 81 refs. The purpose of this review is 3-fold: to briefly discuss epidemiol. evidence that links **antioxidants**, e.g., .beta.-carotene, and vitamin E, to cardiovascular effects; to summarized the oxidn. hypothesis, of **atherosclerosis** and its implication that natural **antioxidants** may be able to **prevent** or slow the progression of **atherosclerosis**; and to review recent studies that test the ability of vitamin E and .beta.-carotene to inhibit the oxidn. of low-d. lipoprotein in vitro.

IT **59-02-9**, .alpha.-Tocopherol
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(.alpha.-tocopherol, .beta.-carotene, and **oxidative** modification of **human** low-d. lipoprotein)
RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 18 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:479453 CAPLUS
DOCUMENT NUMBER: 127:185555
TITLE: .alpha.-Tocopheryl hydroquinone is an efficient multifunctional inhibitor of radical-initiated **oxidation** of low density lipoprotein lipids

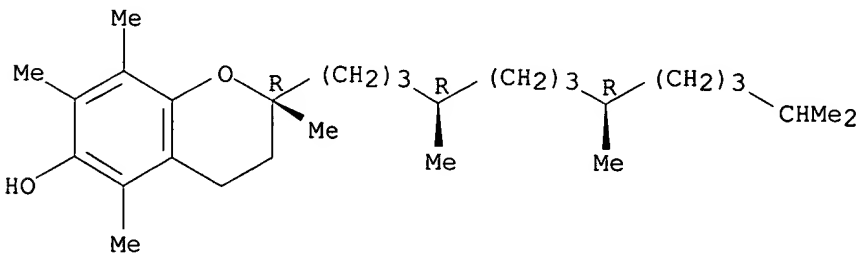
AUTHOR(S): Neuzil, Jiri; Witting, Paul K.; Stocker, Roland
CORPORATE SOURCE: Biochemistry Unit, Heart Research Institute, Camperdown, 2050, Australia
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1997), 94(15), 7885-7890
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB As the oxidn. of low d. lipoprotein (**LDL**) lipids may be a key event in atherogenesis, there is interest in **antioxidants** as potential anti-atherogenic compds. Here we report that .alpha.-tocopheryl hydroquinone (.alpha.-TQH2) strongly inhibited or completely **prevented** the (per)oxidn. of ubiquinol-10 (CoQ10H2), .alpha.-tocopherol (.alpha.-TOH), and both surface and core lipids in **LDL** exposed to either aq. or lipophilic peroxyl radicals, Cu2+, soybean lipoxygenase, or the transition metal-contg. Ham's F-10 medium in the absence or presence of **human** monocyte-derived macrophages. The **antioxidant** activity of .alpha.-TQH2 was superior to that of several other lipophilic hydroquinones, including endogenous CoQ10H2, which is regarded as **LDL**'s first line of **antioxidant** defense. At least three independent activities contributed to the **antioxidant** action of .alpha.-TQH2. First, .alpha.-TQH2 readily assocd. with **LDL** and instantaneously reduced the lipoprotein's ubiquinone-10 to CoQ10H2, thereby maintaining this **antioxidant** in its active form. Second, .alpha.-TQH2 directly intercepted aq. peroxyl radicals, as indicated by the increased rate of its consumption with increasing rates of radical prodn., independent of **LDL**'s content of CoQ10H2 and .alpha.-TOH. Third, .alpha.-TQH2 rapidly quenched .alpha.-tocopheroxyl radical in oxidizing **LDL**, as demonstrated directly by ESR spectroscopy. Similar **antioxidant** activities were also seen when .alpha.-TQH2 was added to high-d. lipoprotein or the protein-free Intralipid, indicating that the potent **antioxidant** activity of .alpha.-TQH2 was neither lipoprotein specific nor dependent on proteins. These results suggest that .alpha.-TQH2 is a candidate for a therapeutic lipid-sol. **antioxidant**. As .alpha.-tocopherylquinone is formed in vivo at sites of **oxidative** stress, including **human atherosclerotic** plaque, and biol. systems exist that reduce the quinone to the hydroquinone, our results also suggest that .alpha.-TQH2 could be a previously unrecognized natural **antioxidant**.

IT **59-02-9**, .alpha.-Tocopherol
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(.alpha.-Tocopheryl hydroquinone inhibits radical-initiated oxidn. of low d. lipoprotein lipids)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 19 OF 60 CAPLUS COPYRIGHT 2001 ACS

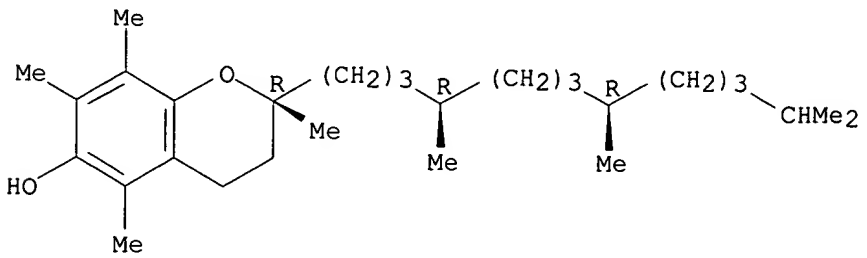
ACCESSION NUMBER: 1997:78978 CAPLUS
DOCUMENT NUMBER: 126:183052
TITLE: **Oxidation** of **LDL** by recombinant **human** 15-lipoxygenase: evidence for .alpha.-tocopherol-dependent **oxidation** of esterified core and surface lipids
AUTHOR(S): Upston, Joanne M.; Neuzil, Jiri; Stocker, Roland
CORPORATE SOURCE: Biochemistry Unit, The Heart Research Institute, Camperdown, NSW 2050, Australia
SOURCE: J. Lipid Res. (1996), 37(12), 2650-2661
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Various lipoxygenases (LO) oxidize low d. lipoprotein (**LDL**) in vitro and 15-LO has been implicated in the development of **atherosclerosis** in vivo. Direct oxidn. of phospholipids (PL) and cholesteryl esters (CE) by LO has been proposed as a mechanism whereby these enzymes cause or contribute to **LDL** lipid peroxidn. Herein we show that the extent to which recombinant **human** 15-LO (rhLO) caused peroxidn. of **LDL**'s esterified core and surface lipids depended on, and directly related to, the .alpha.-tocopherol (.alpha.-TOH) content of the lipoprotein. Thus, CE and PL of in vivo .alpha.-TOH-depleted **LDL**, isolated from a patient with familial isolated vitamin E deficiency, were resistant to oxidn. by rhLO, whereas those in .alpha.-TOH-contg. **LDL** from the same patient receiving vitamin E supplements readily oxidized. The extent to which rhLO caused oxidn. of CE and PL directly and linearly correlated with **LDL**'s content of vitamin E, as demonstrated by studies with in vitro .alpha.-TOH-depleted lipoproteins. The geometric isomers of oxidized cholesteryl linoleate formed in **LDL** during oxidn. initiated by rhLO, matched those obtained during non-enzymic, peroxyl radical-initiated oxidn. of **LDL** while .alpha.-TOH was present. Ascorbate, an efficient co-**antioxidant** for .alpha.-TOH, completely **prevented** rhLO-initiated oxidn. of **LDL**'s CE, but did not inhibit rhLO-mediated oxidn. of unesterified linoleate. These results are inconsistent with direct oxidn. of **LDL** esterified lipids by rhLO. Isolated **LDL** contained free fatty acids (FFA), and its exposure to rhLO caused a rapid formation of linoleate hydroperoxide. To reconcile these data, we propose that during rhLO-initiated oxidn. of **LDL**, enzymic oxidn. of FFA precedes the oxidn. of CE and PL, which occurs largely via a tocopherol-dependent process.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(.alpha.-tocopherol-dependent oxidn. of esterified core and surface lipids)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



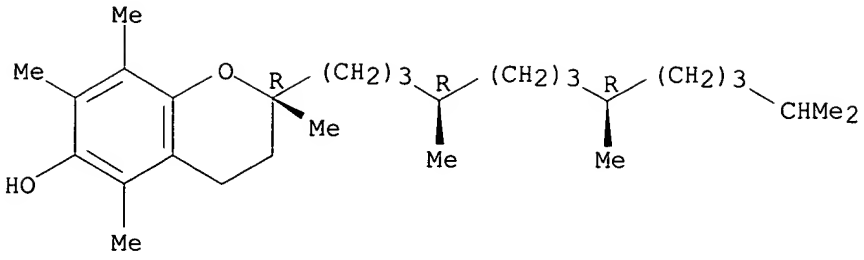
L22 ANSWER 20 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:733264 CAPLUS
DOCUMENT NUMBER: 126:18232
TITLE: .alpha.-Tocopherol inhibits aggregation of **human** platelets by a protein kinase C-dependent mechanism
AUTHOR(S): Freedman, Jane E.; Farhat, John H.; Loscalzo, Joseph; Keaney, John F. Jr
CORPORATE SOURCE: School Medicine, Boston (Mass) University, Boston, MA, 02118-2394, USA
SOURCE: Circulation (1996), 94(10), 2434-2440
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epidemiol. studies indicate that vitamin E (.alpha.-tocopherol) exerts a beneficial effect on cardiovascular disease. The effect of vitamin E has generally been attributed to its **antioxidant** activity and the **antioxidant** protection of **LDL**. Distinct from its effect on **LDL**, vitamin E is also known to inhibit platelet aggregation and adhesion in vitro, but the mechanism(s) responsible for these observations are not known. Using gel-filtered platelets derived from platelet-rich plasma **treated** with .alpha.-tocopherol (500 .mu.mol/L) or vehicle (0.5% ethanol), we found that inhibition of platelet aggregation by .alpha.-tocopherol was closely linked to its incorporation into platelets (r=-.78; P<.02). Platelet incorporation of .alpha.-tocopherol was assocd. with a significant redn. in platelet sensitivity to aggregation by ADP, arachidonic acid, and phorbol ester (PMA) by approx. 0.15-, 2-, and 100-fold, resp. In contrast, platelets **treated** similarly with butylated hydroxytoluene, another potent lipid-sol. **antioxidant**, did not demonstrate any change in sensitivity to these agents. Platelet incorporation of .alpha.-tocopherol inhibited PMA-induced stimulation of platelet protein kinase C (PKC) as detd. by phosphyorylation of the 47-kD PKC substrate. In 15 normal subjects, oral supplementation with .alpha.-tocopherol (400 to 1200 IU/d) resulted in an increase in platelet .alpha.-tocopherol content that correlated with marked inhibition of PMA-mediated platelet aggregation (r=.67; P<.01). Platelets derived from these subjects after supplementation also demonstrated apparent complete inhibition of PKC stimulation by PMA. These data indicate that platelet incorporation of .alpha.-tocopherol at levels attained with oral supplementation is assocd. with inhibition of platelet aggregation through a PKC-dependent mechanism. These observations may represent one potential mechanism for the obsd. beneficial effect of .alpha.-tocopherol in **preventing** the development of coronary artery disease.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(.alpha.-tocopherol inhibits aggregation of **human** platelets by a protein kinase C-dependent mechanism)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

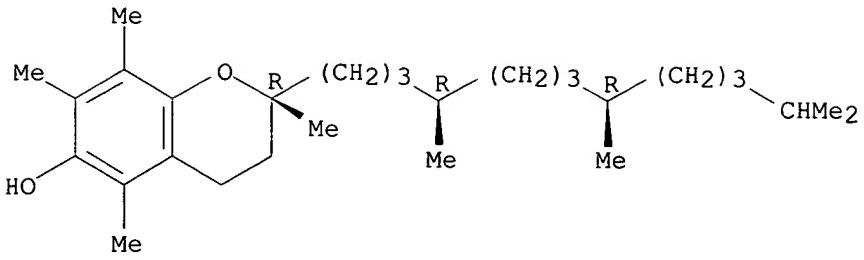


L22 ANSWER 21 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:570481 CAPLUS
DOCUMENT NUMBER: 125:244569
TITLE: Contribution of .alpha.-tocopherol in HDL3 to inhibition of **LDL oxidation** by **human** macrophages
AUTHOR(S): Graham, Annette; Owen, James S.
CORPORATE SOURCE: Academic Dep. of Medicine, Royal Free Hospital School of Medicine, London, NW3 2PF, UK
SOURCE: Biochem. Soc. Trans. (1996), 24(3), 396S
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epidemiol. studies have established an inverse relationship between plasma concns. of high-d. lipoprotein (HDL) and the risk of coronary heart disease. HDL may act as an **antioxidant** particle, protecting against the oxidn. of low-d. lipoprotein; **oxidative** modifications of **LDL** allow recognition by the macrophage scavenger receptor and result in the unregulated accumulation of intracellular cholesteryl esters within the developing **atherosclerotic** plaque. Oxidn. of **LDL** can be influenced by its .alpha.-tocopherol content, and this **antioxidant** vitamin can partition readily between plasma lipoproteins. To define the role of HDL3-derived .alpha.-tocopherol in **prevention** of **LDL** oxidn., the authors isolated **human** HDL3 and compared the inhibitory effects of this lipoprotein with partially delipidated HDL3 on .alpha.-tocopherol depletion and **LDL** oxidn. by **human** macrophages. In the presence of macrophages, .alpha.-tocopherol was readily lost from **LDL**, with 90% depletion occurring at around 4-6 h; in the absence of cells, depletion was modest. Addn. of HDL3 supplemented the medium with .alpha.-tocopherol and significantly decreased depletion of .alpha.-tocopherol from the medium at 3 h. Early stages of **LDL** oxidn. monitored by increases in peroxide content of the entire medium, or by increases in **LDL** particle electrophoretic mobility, were inhibited by HDL3.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(contribution of .alpha.-tocopherol in HDL3 to inhibition of **LDL** oxidn. by **human** macrophages)
RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 22 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:330142 CAPLUS
DOCUMENT NUMBER: 125:32484
TITLE: Cosupplementation with coenzyme Q **prevents** the **prooxidant** effect of .alpha.-tocopherol and increases the resistance of **LDL** to transition metal-dependent **oxidation** initiation
AUTHOR(S): Thomas, Shane R.; Neuzil, Jiri; Stocker, Roland
CORPORATE SOURCE: Biochemistry Group, Heart Research Institute, Sydney, 2050, Australia
SOURCE: Arterioscler., Thromb., Vasc. Biol. (1996), 16(5), 687-696
CODEN: ATVBFA; ISSN: 1079-5642
DOCUMENT TYPE: Journal
LANGUAGE: English

AB There is considerable interest in the ability of **antioxidant** supplementation, in particular with vitamin E, to attenuate **LDL** oxidn., a process implicated in atherogenesis. Since vitamin E can also promote **LDL** lipid peroxidn., we investigated the effects of supplementation with vitamin E alone or in combination with coenzyme Q on the early stages of the oxidn. of isolated **LDL**. Isolated **LDL** was obtained from healthy subjects before and after in vitro enrichment with vitamin E (D-.alpha.-tocopherol, .alpha.-TOH) or dietary supplementation with D-.alpha.-TOH (1 g/d) and/or coenzyme Q (100 mg/d). **LDL** oxidn. initiation was assessed by measurement of the consumption of .alpha.-TOH and cholesteryl esters contg. polyunsatd. fatty acids and the accumulation of cholesteryl ester hydroperoxides during incubation of **LDL** in the transition metal-contg. Ham's F-10 medium in the absence and presence of **human** monocyte-derived macrophages (MDMs). Native **LDL** contained 8.5.+-.2 mols. of .alpha.-TOH and 0.5 to 0.8 mols. of ubiquinol-10 (CoQ10H2, the reduced form of coenzyme Q) per lipoprotein particle. Incubation of this **LDL** in Ham's F-10 medium resulted in a time-dependent loss of .alpha.-TOH with concomitant stoichiometric conversion of the major cholesteryl esters to their resp. hydroperoxides. MDMs enhanced this process. **LDL** lipid peroxidn. occurred via a radical chain reaction in the presence of .alpha.-TOH, and the rate of this oxidn. decreased on .alpha.-TOH depletion. In vitro enrichment of **LDL** with .alpha.-TOH resulted in an **LDL** particle contg. sixfold to sevenfold more .alpha.-TOH, and such enriched **LDL** was more readily oxidized in the absence and presence of MDMs compared with native **LDL**. In vivo .alpha.-TOH-deficient **LDL**, isolated from a patient with familial isolated vitamin E deficiency, was highly resistant to Ham's F-10-initiated oxidn., whereas dietary supplementation with vitamin E restored the oxidizability of the patient's **LDL**. Oral supplementation of healthy individuals for 5 days with either .alpha.-TOH or coenzyme Q increased the **LDL** levels of .alpha.-TOH and CoQ10H2 by two to three or three to four times, resp. .alpha.-TOH-supplemented **LDL** was significantly more prone to oxidn., whereas CoQ10H2-enriched **LDL** was more resistant to oxidn. initiation by Ham's F-10 medium than native **LDL**.

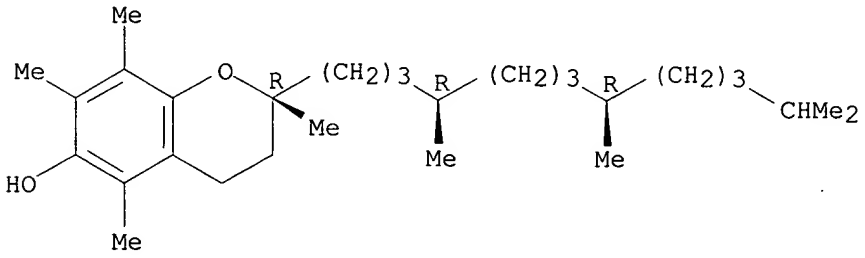
Cosupplementation with both .alpha.-TOH and coenzyme Q resulted in **LDL** with increased levels of .alpha.-TOH and CoQ10H2, and such **LDL** was markedly more resistant to initiation of oxidn. than native or .alpha.-TOH-enriched **LDL**. These results demonstrate that oral supplementation with .alpha.-TOH alone results in **LDL** that is more prone to oxidn. initiation, whereas cosupplementation with coenzyme Q not only **prevents** this **prooxidant** activity of vitamin E but also provides the lipoprotein with increased resistance to oxidn.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(cosupplementation with coenzyme Q **prevents** the **prooxidant** effect of .alpha.-tocopherol and increases the resistance of **LDL** to transition metal-dependent oxidn. initiation)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 23 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:975158 CAPLUS

DOCUMENT NUMBER: 124:83058

TITLE: **Oxidative** modification and **antioxidant** protection of **human** low density lipoprotein at high and low oxygen partial pressures

AUTHOR(S): Hatta, Akira; Frei, Balz

CORPORATE SOURCE: Whitaker Cardiovascular Inst., Univ. School of Medicine, Boston, MA, 02118, USA

SOURCE: J. Lipid Res. (1995), 36(11), 2383-93
CODEN: JLPRAW; ISSN: 0022-2275

DOCUMENT TYPE: Journal

LANGUAGE: English

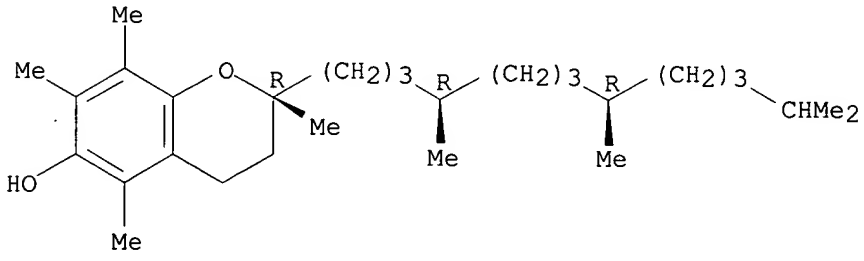
AB **Oxidative** modification of low d. lipoprotein (**LDL**) in the subendothelial space of the arterial wall has been implicated as an initial process in **atherosclerosis**. In vitro studies of **LDL** oxidn. are usually done at ambient oxygen partial pressure (pO2; approx. 160 torr, or 21% O2), which is considered higher than arterial tissue pO2 (30-70 torr, and as low as 20 torr, or 2.5% O2, in **atherosclerotic** lesions). In addn., .beta.-carotene acts as an efficient free radical scavenger only at low pO2. Therefore, the authors investigated the effects of high (20%) and low (2%) pO2 on the kinetics of **LDL** oxidn., and the effectiveness of .beta.-carotene compared to other physiol. **antioxidants** in **preventing LDL** oxidn. At low pO2, the rate of Cu2+-induced **oxidative** modification of **LDL** was lower than at high pO2. Furthermore, at high pO2 there was a distinct lag phase preceding the propagation of lipid peroxidn. in Cu2+-exposed **LDL**, as measured by cholesteryl ester hydroperoxide formation; in contrast, there appeared to be no distinct

peroxidn. lag phase in **LDL** incubated with Cu2+ at low pO2. Elevating .alpha.-tocopherol levels in **LDL** about 5-fold resulted in significant **antioxidant** protection: the lipid peroxidn. lag phase at high pO2 increased by 45% (from 58 to 84 min), and the initial rate (0-1 h) of lipid hydroperoxide formation at low pO2 was reduced by 52% (from 11.6 to 5.6 nmol/mg **LDL** protein/h). In contrast, increasing **LDL** .beta.-carotene levels about 6-fold did not inhibit **LDL** oxidn. at either pO2. Most remarkably, low concns. of ascorbic acid (30 .mu.M) drastically reduced **LDL** oxidn., regardless of PO2: the lipid peroxidn. lag phase at high pO2 increased more than 7-fold (from 46 min to >360 min), and at low pO2 no lipid hydroperoxides could be detected for at least 6 h of incubation. These results show that at low physiol. pO2, Cu2+-induced **LDL** oxidn. occurs at a significantly lower rate than at ambient pO2. At both high and low pO2, .beta.-carotene cannot inhibit **LDL** oxidn., whereas .alpha.-tocopherol has a moderate protective effect, and low physiol. concns. of ascorbic acid very strongly suppress **LDL** oxidn.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**oxidative** modification and **antioxidant** protection of **human** low-d. lipoprotein at high and low oxygen partial pressures)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 24 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:904299 CAPLUS
DOCUMENT NUMBER: 124:172220
TITLE: **Prevention** of cholesteryl ester accumulation in P388D1 macrophage-like cells by increased cellular vitamin E depends on species of extracellular cholesterol. Conventional heterologous non-**human** cell cultures are poor models of **human atherosclerotic** foam cell formation
AUTHOR(S): Asmis, Reto; Llorente, Vicenta C.; Gey, K. Fred
CORPORATE SOURCE: Inst. Biochem. Molecular Biol., Univ. Berne, Switz.
SOURCE: Eur. J. Biochem. (1995), 233(1), 171-8
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To study the cellular role of the anti-**oxidative** vitamins in the formation of foam cells has not yet been studied in detail, the effect of .alpha.-tocopherol (I) and ascorbic acid (II) loading of P388D1 macrophage-like cells on their cholesterol and cholesteryl ester levels and their response to the exposure to different lipoproteins was investigated. I loading, but not II loading, of P388D1 cells strongly reduced their cellular cholesteryl ester/cholesterol ratio (the crucial

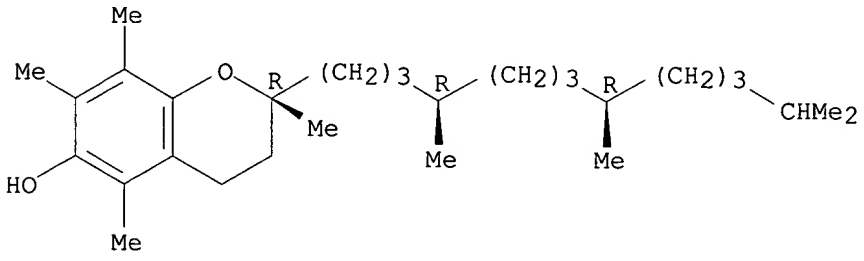
indicator of foam cell formation) when fetal calf serum was the only extracellular source of cholesterol. This effect of I was mainly due to a reduced uptake of fetal calf serum-derived cholesterol. I loading, however, did not reduce the cholesteryl ester/cholesterol ratio when **human** unmodified low-d. lipoprotein (**LDL**) was added to culture medium contg. fetal calf serum. Thus, the uptake of fetal calf serum-derived cholesterol was competitively reduced by **human LDL**, the uptake of which remained unaffected by I. Similarly, I loading did not **prevent** cholesteryl ester formation induced by **human LDL** either oxidized with Cu2+, UV light or HOCl, or modified by acetylation, aggregation, or by malondialdehyde **treatment**. The present exptl. conditions lacked any pro-**oxidative** burden, since (a) II, either alone or combined with I, did not affect cellular cholesteryl ester levels, (b) foam cell formation was not a linear function of the degree of **oxidative LDL** modification, and (c) I lacked specific effects on **oxidatively** modified **LDL**. Thus, the redn. of cellular cholesteryl esters by I in the absence of **human** unmodified **LDL** was hardly due to common anti-**oxidative** properties of vitamin E. In conclusion, a desirable I effect on the cholesteryl ester balance in mouse tumor-derived P388D1 cells strongly depended on the species of extracellular cholesterol carrier, cautions against premature generalizations of conventional non-**human** cell culture data.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(the effect of .alpha.-tocopherol on cholesteryl ester balance in mouse P388D1 macrophage-like cells depended on the species of extracellular cholesterol carrier)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 25 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:858256 CAPLUS

DOCUMENT NUMBER: 123:282454

TITLE: **Human** suction blister interstitial fluid **prevents** metal ion-dependent **oxidation** of low density lipoprotein by macrophages and in cell-free systems

AUTHOR(S): Dabbagh, Alya J.; Frei, Balz

CORPORATE SOURCE: Whitaker Cardiovascular Inst., Boston Univ. School of Medicine, Boston, MA, 02118, USA

SOURCE: J. Clin. Invest. (1995), 96(4), 1958-66
CODEN: JCINAO; ISSN: 0021-9738

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **LDL** in the circulation is well-protected against oxidn. by the highly efficient **antioxidant** defense mechanism of **human** plasma. **LDL** oxidn. contributing to **atherosclerosis**,

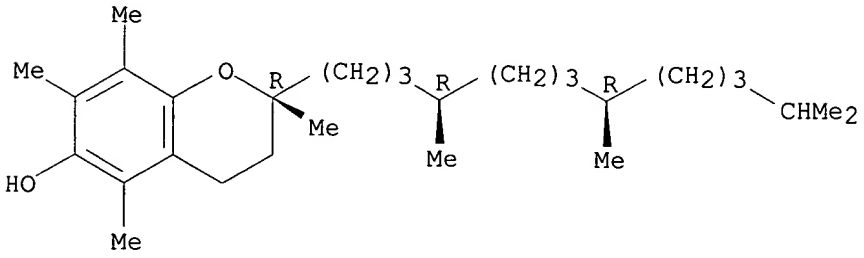
therefore, has been hypothesized to take place in the interstitial fluid of the arterial wall. The authors investigated the **antioxidant** compn. and the capacity to inhibit **LDL** oxidn. of **human** suction blister interstitial fluid (SBIF), a suitable representative of interstitial fluid. The authors found that the concns. in SBIF of the aq. small-mol. **antioxidants** ascorbate and urate were, resp., higher and identical to plasma concns. In contrast, lipoprotein-assocd. lipids and lipid-sol. **antioxidants** (.alpha.-tocopherol, ubiquinol-10, lycopene, and .beta.-carotene) were present at only 8-23% of the concns. in plasma. No lipid hydroperoxides could be detected (<5 nM) in either fluid. The capacity of serum and SBIF to protect **LDL** from oxidn. was investigated in three metal ion-dependent systems: copper, iron, and murine macrophages in Ham's F-10 medium. In all three systems, addn. of .gtoreq.6% (vol./vol.) of either serum or SBIF inhibited **LDL** oxidn. by >90%. The concn. that inhibited macrophage-mediated **LDL** oxidn. by 50% was as low as 0.3% serum and 0.7% SBIF. The enzymic or phys. removal of ascorbate or urate and other low-mol.-wt. components did not affect the ability of either fluid to **prevent** **LDL** oxidn., and the high-mol.-wt. fraction was as protective as whole serum or SBIF. Thus, both serum and SBIF very effectively protect **LDL** from metal ion-dependent oxidn., most probably because of a cumulative metal-binding effect of several proteins. The data suggest that **LDL** in the interstitial fluid of the arterial wall is very unlikely to get modified by metal ion-mediated oxidn.

IT **59-02-9**, .alpha.-Tocopherol
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(**human** arterial wall interstitial fluid **prevents** metal ion-dependent oxidn. of **LDL** by macrophages which indicates that **LDL** oxidn. contributing to **atherosclerosis** probably does not occur in the arterial wall interstitial fluid)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 26 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:791016 CAPLUS

DOCUMENT NUMBER: 123:224825

TITLE: **Antioxidative** activity of ubiquinol-10 at physiologic concentrations in **human** low density lipoprotein

AUTHOR(S): Kontush, Anatol; Huebner, Christoph; Finckh, Barbara; Kohlschuetter, Alfried; Beisiegel, Ulrike

CORPORATE SOURCE: Medical Clinic, University of Hamburg, Hamburg, Germany

SOURCE: Biochim. Biophys. Acta (1995), 1258(2), 177-87
CODEN: BBACAQ; ISSN: 0006-3002

DOCUMENT TYPE: Journal

LANGUAGE: English

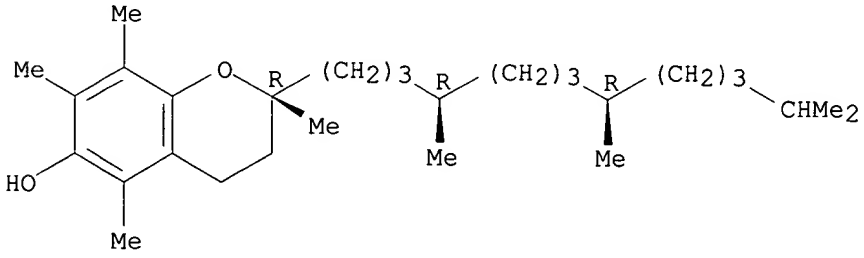
AB Ubiquinol-10 is a powerful lipid-sol. **antioxidant** found in cell membranes and lipoproteins in vivo. Its mechanism of action on lipid peroxidn. has been detd. in model and biol. systems. Data concerning anti-**oxidative** activity of ubiquinol-10 in lipoproteins, however, are still controversial. The present work examines its role in the **prevention** of low d. lipoprotein (**LDL**) oxidn., specifically its influence on a copper-mediated **oxidative** modification of **human LDL** in vitro. The authors found that ubiquinol-10 incorporated in **LDL** in subnormal concns. (0.05-0.13 mol/mol **LDL** incorporated in comparison with 0.10-1.20 mol/mol **LDL** reported as normally in **human LDL**) slightly but not significantly decreased prodn. of lipid peroxidn. products (lipid peroxides, conjugated dienes, thiobarbituric acid-reactive substances) during the first hours of oxidn. The extent of apolipoprotein B modification (**LDL** fluorescence at 360/430 nm) was also decreased. Increasing the ubiquinol-10 concn. in **LDL** to 0.55-1.48 mol/mol **LDL** made it significantly more resistant to copper-mediated oxidn. than native **LDL**. Adding the same amts. of either ubiquinone-10 or .alpha.-tocopherol to the **LDL** suspension had almost no effect on its oxidn. Ubiquinol-10 decreased .alpha.-tocopherol consumption during **LDL** oxidn. and was consumed more rapidly than the latter. These results demonstrate that **LDL** ubiquinol-10 content is an important factor influencing **LDL** susceptibility to oxidn. by copper and suggest that it represents the first line of defense against **oxidative** modification in **human LDL**.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(ubiquinol-10 enhances anti-**oxidative** activity for **human** low-d. lipoproteins of)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 27 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:739078 CAPLUS

DOCUMENT NUMBER: 123:142520

TITLE: Vitamin C **prevents** metal ion-dependent initiation and propagation of lipid **peroxidation** in **human** low-density lipoprotein

AUTHOR(S): Retsky, Karen L.; Frei, Balz

CORPORATE SOURCE: Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA, USA

SOURCE: Biochim. Biophys. Acta (1995), 1257(3), 279-87
CODEN: BBACAQ; ISSN: 0006-3002

DOCUMENT TYPE: Journal

LANGUAGE: English

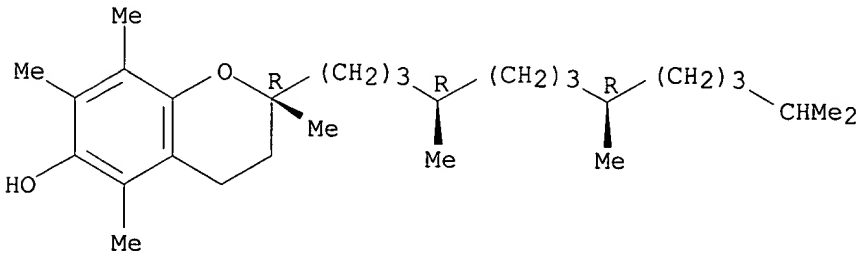
AB Lipid peroxidn. and **oxidative** modification of low-d. lipoprotein (**LDL**) have been implicated as causal factors in the pathogenesis of **atherosclerosis**, and **prevention** of **LDL** oxidn. by **antioxidants** may be an effective strategy to inhibit the progression of the disease. We investigated the effects of the reduced form of vitamin C (L-ascorbic acid, AA) and its two-electron oxidn. product (dehydro-L-ascorbic acid, DHA) upon metal ion-dependent **oxidative** modification of **human LDL**. We found that low micromolar concns. of both AA and DHA protect **LDL** against oxidn. induced by Cu2+ or by hemin and hydrogen peroxide. In a dose-dependent manner, AA and DHA **prevented** the initiation of lipid peroxidn. in **LDL**, as detd. by a sensitive and selective assay for lipid hydroperoxides utilizing HPLC with chemiluminescence detection. AA and DHA also preserved the **LDL**-assocd. **antioxidants** .alpha.-tocopherol, .beta.-carotene, and lycopene, but not ubiquinol-10. Furthermore, AA was able to stop propagation of lipid peroxidn. in **LDL**, whereas DHA lacked this ability. The addn. of 60 .mu.M AA to **LDL** contg. up to 38 nmol/mg protein of pre-formed lipid hydroperoxides led to their rapid disappearance; this activity of AA was dependent on the presence of redox-active copper, but did not lead to the formation of lipid hydroxides, the reduced form of lipid hydroperoxides. The data show that in Cu2+-exposed **LDL** (i) vitamin C primarily spares, rather than regenerates, .alpha.-tocopherol and other endogenous **antioxidants**, except for ubiquinol-10; (ii) AA and DHA, unlike the **LDL**-assocd. **antioxidants**, act as **preventive** rather than chain-breaking **antioxidants**, i.e., AA and DHA **prevent** initiation of lipid peroxidn. in **LDL**; and (iii) AA can terminate lipid peroxidn., thereby protecting partially oxidized **LDL** against further **oxidative** modification.

IT **59-02-9**, .alpha.-Tocopherol
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(vitamin C **prevents** metal ion-dependent initiation and propagation of lipid peroxidn. in **human** low-d. lipoprotein and preserves other **antioxidants**)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 28 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:444432 CAPLUS

DOCUMENT NUMBER: 122:233531

TITLE: **Prevention** of tocopherol-mediated **peroxidation** in ubiquinol-10-free **human** low density-lipoprotein

AUTHOR(S): Bowry, Vincent W.; Mohr, Detlef; Cleary, Janelle; Stocker, Roland

CORPORATE SOURCE: Biochem. Group, Heart Res. Inst., Camperdown, Sydney, 2050, Australia

SOURCE: J. Biol. Chem. (1995), 270(11), 5756-63

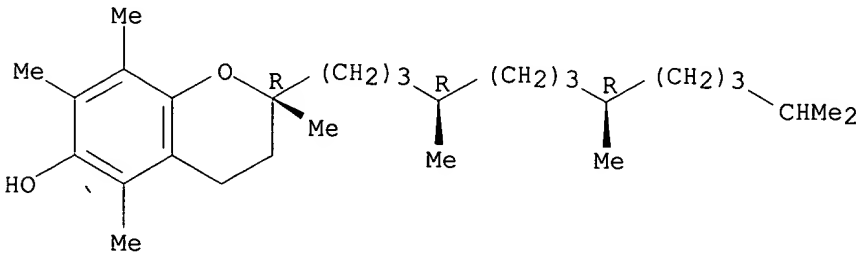
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oxidn. of low d. lipoprotein (**LDL**) may be involved in the development of **atherosclerosis**. It has recently been shown that .alpha.-tocopherol (.alpha.-TOH) can act either as an **antioxidant** or **prooxidant** for isolated low d. lipoprotein (**LDL**). In the absence of an effective co-**antioxidant**, .alpha.-TOH is a **prooxidant** and this activity is evidently due to reaction of the .alpha.-tocopheroxyl radical (.alpha.-TO.) with the **LDL**'s polyunsatd. lipids (Bowry, V. B., and Stocker, R. (1993) J. Am. Chem. Soc. 115, 6029-6045). Herein we examd. the effectiveness of selected natural and synthetic radical scavengers as co-**antioxidants** for inhibiting peroxyl radical-induced peroxidn. in **LDL** that is devoid of ubiquinol-10 (an effective endogenous co-**antioxidant**) but still contains most of its natural complement of .alpha.-TOH. Various quinols, catechols, and aminophenols, as well as ascorbate, 6-palmityl ascorbate, and bilirubin, were very effective co-**antioxidants** under our test conditions, whereas ordinary phenolic **antioxidants**, including short-tailed .alpha.-TOH homologues, were less effective. Reduced glutathione, urate, and Probucol were ineffective. These findings confirm that the **prooxidant** activity of .alpha.-TOH in **LDL** relies heavily on the segregation of water-insol. radicals (particularly .alpha.-TO.) into individual **LDL** particles, since it was those compds. that are expected to either irreversibly reduce .alpha.-TO. or accelerate the diffusion of radicals between particles which most effectively inhibited the tocopherol-mediated phase of peroxidn. Theor. and practical implications of these findings are discussed, as is their relevance of the "**LDL** oxidn." hypothesis of atherogenesis.

IT **59-02-9**, .alpha.-Tocopherol
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(**prevention** of tocopherol-mediated peroxidn. in ubiquinol-10-free **human** low d.-lipoprotein)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 29 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:698260 CAPLUS
DOCUMENT NUMBER: 121:298260
TITLE: **Human** (THP-1) macrophages oxidize **LDL** by a thiol-dependent mechanism
AUTHOR(S): Graham, Annette; Wood, Jenny L.; O'Leary, Vanessa J.; Stone, David
CORPORATE SOURCE: Department of Biochemical Sciences, Wellcome Research Laboratories, Beckenham/Kent, BR3 3BS, UK
SOURCE: Free Radical Res. (1994), 21(5), 295-308
CODEN: FRARER; ISSN: 1071-5762

DOCUMENT TYPE: Journal
LANGUAGE: English

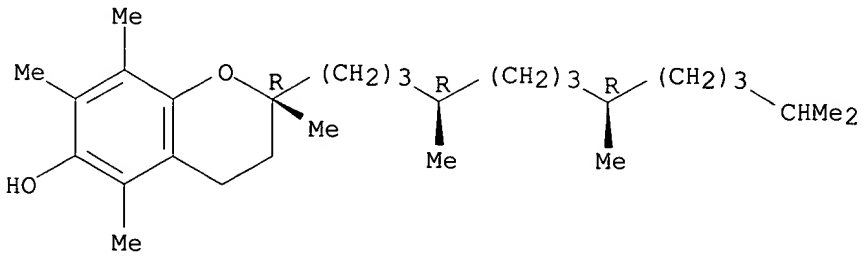
AB The **oxidative** modification of low-d. lipoprotein by macrophages may be an important mechanism in the pathogenesis of **atherosclerosis**. The **human** monocytic leukemia cell line THP-1, when stimulated with phorbol ester, shares many properties with **human** monocyte-derived macrophages. Oxidn. of **LDL** by these cells was characterized by depletion of .alpha.-tocopherol, increases in thiobarbituric acid reactive substances and increases in electrophoretic mobility. The **LDL** particles were also converted to a form which increased accumulation of cholesteryl esters within macrophages. Oxidn. of **LDL** by these cells was characterized by depletion of .alpha.-tocopherol, increases in thiobarbituric acid reactive substances and increases in electrophoretic mobility. The **LDL** particles were also converted to a form which increased accumulation of cholesteryl esters within macrophages. The **oxidative** mechanism appeared to be dependent upon the presence of thiols in the cellular medium. Oxidn. of **LDL** by THP-1 macrophages, and prodn. of thiols by these cells, were dependent upon the presence of L-cystine in the medium. Furthermore, cellular oxidn. of **LDL** could be partially mimicked by the addn. of cysteine to Hams F10 medium. Macrophage-independent oxidn. of **LDL**, mediated by the addn. of copper ions, was inhibited by cystine and cysteine in phosphate buffered saline, but not in Hams F10 medium. The glutathione content of THP-1 macrophages was also dependent upon the presence of cysteine or cystine in the medium, but inhibition of glutathione synthesis by buthionine sulfoximine did not **prevent** the prodn. of thiols or the oxidn. of **LDL** by THP-1 macrophages.

IT **59-02-9**, .alpha.-Tocopherol
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(of macrophage; low-d. lipoprotein oxidn. by **human** macrophages by thiol-dependent mechanism in relation to **atherosclerosis**)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 30 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:321929 CAPLUS
Correction of: 1994:268899

DOCUMENT NUMBER: 120:321929
Correction of: 120:268899

TITLE: Low-dose .alpha.-tocopherol improves and high-dose .alpha.-tocopherol worsens endothelial vasodilator function in cholesterol-fed rabbits.

AUTHOR(S): Keaney, John F., Jr.; Gaziano, J. Michael; Xu, Aiming; Frei, Balz; Curran-Celentano, Joanne; Shwaery, Glenn T.; Loscalzo, Joseph; Vita, Joseph A.

CORPORATE SOURCE: Dep. Med., Brigham and Women's Hosp., Boston, MA,

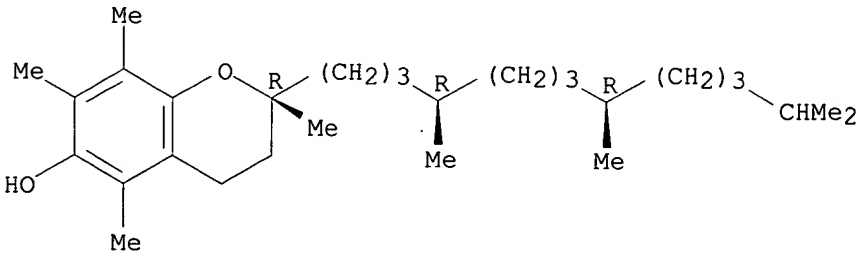
02115, USA
SOURCE: J. Clin. Invest. (1994), 93(2), 844-51
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Abnormalities in endothelium-dependent arterial relaxation develop early in **atherosclerosis** and may, in part, result from the effects of modified low-d. lipoprotein (**LDL**) on agonist-mediated endothelium-derived relaxing factor release and degrdn. .alpha.-Tocopherol (AT) is the main lipid-sol. **antioxidant** in **human** plasma and lipoproteins. Therefore, the effects of AT on endothelium-dependent arterial relaxation were investigated in male New Zealand White rabbits fed diets contg. no additive (controls), 1% cholesterol (cholesterol group), or 1% cholesterol with either 1000 IU AT/kg chow (low-dose AT group) or 10,000 IU AT/kg chow (high-dose AT group). After 28 days, endothelial function and **LDL** susceptibility to ex vivo Cu-mediated oxidn. were assayed. Acetylcholine- and A23187-mediated endothelium-dependent relaxations were significantly impaired in the cholesterol group but preserved in the low-dose AT group. Compared to the control and cholesterol groups, vessels from the high-dose AT group demonstrated profound impairment of arterial relaxation and significantly more intimal proliferation than the other groups. In normal vessels, AT had no effect on endothelial function. **LDL** derived form both the high- and low-dose AT groups was more resistant to oxidn. than **LDL** from control animals. These data indicate that modest dietary **treatment** with AT preserves endothelial vasodilator function in cholesterol-fed rabbits, while a higher dose of AT is assocd. with endothelial dysfunction and enhanced intimal proliferation despite continued **LDL** resistance to ex vivo Cu-mediated oxidn.

IT **59-02-9**
RL: PRP (Properties)
(endothelial vasodilator function response to dietary cholesterol and level of)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 31 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:443469 CAPLUS
DOCUMENT NUMBER: 119:43469
TITLE: Tocopherol-mediated **peroxidation**. The **prooxidant** effect of vitamin E on the radical-initiated **oxidation** of **human** low-density lipoprotein
AUTHOR(S): Bowry, Vincent W.; Stocker, Roland
CORPORATE SOURCE: Biochem. Group, Heart Res. Inst., Sydney, 2050, Australia
SOURCE: J. Am. Chem. Soc. (1993), 115(14), 6029-44
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal

LANGUAGE: English

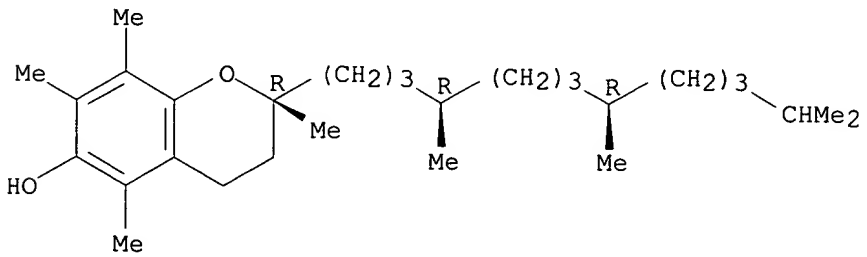
AB Oxidn. of **human** low-d. lipoprotein (**LDL**) is implicated as an initiator of **atherosclerosis**. .alpha.-Tocopherol (.alpha.-TocH) may thus inhibit **atherosclerosis** because it is the major and most active chain-breaking **antioxidant** in extd. **LDL** lipid. These studies show, however, that .alpha.-TocH can be a strong **prooxidant** for the **LDL** itself, i.e., an aq. dispersion of lipid-bearing particles. Thus, a steady flux (Rg) of alkylperoxyl radicals (ROO.bul.) generated from a water-sol. azo initiator-induced lipid peroxidn. in **LDL** which was faster in the presence of .alpha.-TocH than in its absence (for Rg < 2 nM s-1), insensitive to Rg and [O2], and inhibited by vitamin C, ubiquinol-10 (normally present in fresh **LDL**), and small phenolic **antioxidants** but not inhibited by the aq. radical scavenger uric acid. Furthermore, **LDL** peroxidn. induced by a water- or lipid-sol. azo initiator or by transition metals in Ham's F-10 cell culture medium was accelerated by increasing the concn. of .alpha.-TocH in **LDL**. It is proposed that **LDL** peroxidn. is initiated by the reaction of ROO.bul. with .alpha.-TocH and that the inability of the .alpha.-Toc.bul. formed in this reaction to escape from an **LDL** particle then forces .alpha.-Toc.bul. to propagate a radical chain via its reaction with polyunsatd. fatty acids (PUFA) lipid within the particle (.alpha.-Toc.bul. + LH + O2 .fwdarw. .alpha.-TocH + LOO.bul.). Termination of a radical chain occurs when a peroxidizing **LDL** particle captures a second radical from the aq. medium (ROO.bul. + .alpha.-Toc.bul. .fwdarw. nonradical products). Steady-state kinetic anal. of this mechanism yields a theor. model for tocopherol-mediated peroxidn. (TMP) in lipid dispersions which fully explains the findings for **LDL**. Thus, peroxidn. of **LDL** lipid can (only) be **prevented** by agents which eliminate the .alpha.-Toc.bul. radical: vitamin C and **LDL**-assocd. ubiquinol-10 do so by "exporting the radical" into the aq. medium, whereas small phenolic **antioxidants** (e.g., butylrated hydroxytoluene) accelerate the transfer of radicals between particles. The theor. and practical implications of TMP in **LDL**, dispersions, and bulk lipids are discussed.

IT **59-02-9**
RL: BIOL (Biological study)
(lipid peroxidn in low-d. lipoproteins initiation by radicals mediation by, empirical and theor. studies of)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 32 OF 60 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1992:233218 CAPLUS

DOCUMENT NUMBER: 116:233218

TITLE: Increased oxidizability of plasma lipoproteins in diabetic patients can be decreased by probucol therapy and is not due to glycation

AUTHOR(S): Babiy, Alexander V.; Gebicki, Janusz M.; Sullivan,

David R.; Willey, Karen
CORPORATE SOURCE: Sch. Biol. Sci., Macquarie Univ., Sydney, Australia
SOURCE: Biochem. Pharmacol. (1992), 43(5), 995-1000
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

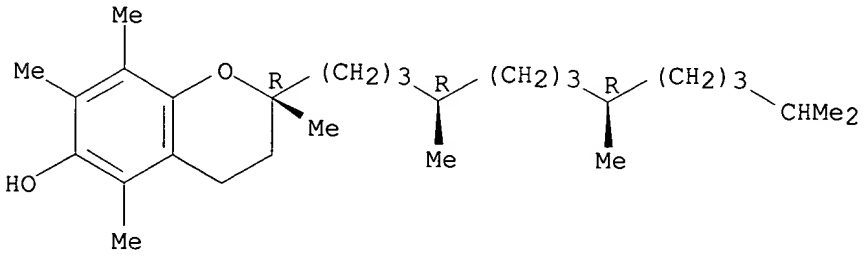
AB **Atherosclerosis** is considered to be the major complication of diabetes mellitus. Since diabetic patients have increased blood levels of lipid peroxidn. products, studies were conducted to det. whether the susceptibility of blood components to oxidn. is altered in this disease. The parameters characterizing the extent of **oxidative** change and the **antioxidant** status of low-d. lipoprotein (**LDL**) and high-d. lipoprotein were analyzed in diabetic patients and in a control population. **LDL** oxidizability was higher for patients than for individuals in the control group. There were no differences in the .alpha.-tocopherol content or levels of performed peroxides in **LDL** samples from diabetic patients and control individuals which could account for this effect. Similarly, **LDL** glycation, common in diabetes mellitus, was not responsible, since **LDL** glycated in vitro was more rather than less resistant to oxidn. Even the presence of unbound glucose at normal or elevated physiol. concns. had a delaying effect on the oxidn. of **LDL**. The increased oxidizability of **LDL** from diabetic patients could be reduced to control levels by a 6-wk std. **treatment** with Probucol, originally administered to reduce blood cholesterol.

IT **59-02-9**, .alpha.-Tocopherol
RL: BIOL (Biological study)
(of low-d. lipoproteins of blood plasma in **human** diabetes)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 33 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:56571 CAPLUS
DOCUMENT NUMBER: 116:56571
TITLE: monocyte transmigration induced by modification of low-density lipoprotein in cocultures of **human** aortic wall cells is due to induction of monocyte chemotactic protein 1 synthesis and is abolished by high-density lipoprotein
AUTHOR(S): Navab, Mahamad; Imes, Susan S.; Hama, Susan Y.; Hough, Gregory P.; Ross, Lori A.; Bork, Richard W.; Valente, Anthony J.; Berliner, Judith A.; Drinkwater, Davis C.; et al.
CORPORATE SOURCE: Sch. Med., Univ. California, Los Angeles, CA, 90024-167917, USA
SOURCE: J. Clin. Invest. (1991), 88(6), 2039-46
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

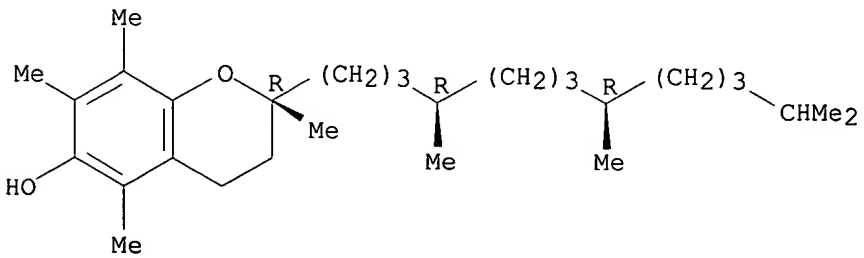
AB Incubation of cocultures of **human** aortic endothelial (HAEC) and smooth muscle cells (HASMC) with low-d. lipoprotein (**LDL**) in the presence of 5-10% **human** serum resulted in a 7.2-fold induction of mRNA for monocyte chemotactic protein 1 (MCP-1), a 2.5-fold increase in the levels of MCP-1 protein in the coculture supernatants, and a 7.1-fold increase in the transmigration of monocytes into the subendothelial space of the cocultures. Monocyte migration was inhibited by 91% by antibody to MCP-1. Media collected from the cocultures that had been incubated with **LDL** induced target endothelial cells (EC) to bind monocyte but not neutrophil-like cells. Media collected from cocultures that had been incubated with **LDL**-induced monocyte migration into the subendothelial space of other cocultures that had not been exposed to **LDL**. In contrast, media from sep. cultures of EC or smooth muscle cells (SMC) contg. equal no. of EC or SMC compared to coculture and incubated with the same **LDL** did not induce monocyte migration when incubated with the target cocultures. High-d. lipoprotein (HDL), when presented to cocultures together with **LDL**, reduced the increased monocyte transmigration by 91%. Virtually all of the HDL-mediated inhibition was accounted for by the HDL2 subfraction. HDL3 was essentially without effect. Apolipoprotein AI was also ineffective in **preventing** monocyte transmigration while phosphatidylcholine liposomes were as effective as HDL2 suggesting that lipid components of HDL2 may have been responsible for its action. Preincubating **LDL** with .beta.-carotene or with .alpha.-tocopherol did not reduce monocyte migration. However, pretreatment of **LDL** with probucol or pretreatment of the cocultures with probucol, .beta.-carotene, or .alpha.-tocopherol before the addn. of **LDL prevented** the **LDL**-induced monocyte transmigration. Addn. of HDL or probucol to **LDL** after the exposure to cocultures did not **prevent** the modified **LDL** from inducing monocyte transmigration in fresh cocultures. The authors conclude that cocultures of **human** aortic cells can modify **LDL** even in the presence of serum, resulting in the induction of MCP-1, and that HDL and **antioxidants prevent** the **LDL**-induced monocyte transmigration.

IT **59-02-9**, .alpha.-Tocopherol
RL: BIOL (Biological study)
(monocyte adhesion to endothelial cells and transmigration responses to high-d. lipoproteins and, **atherosclerosis** pathogenesis in relation to)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 34 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:161349 CAPLUS
DOCUMENT NUMBER: 114:161349
TITLE: Ubiquinol-10 protects **human** low density lipoprotein more efficiently against lipid **peroxidation** than does .alpha.-tocopherol

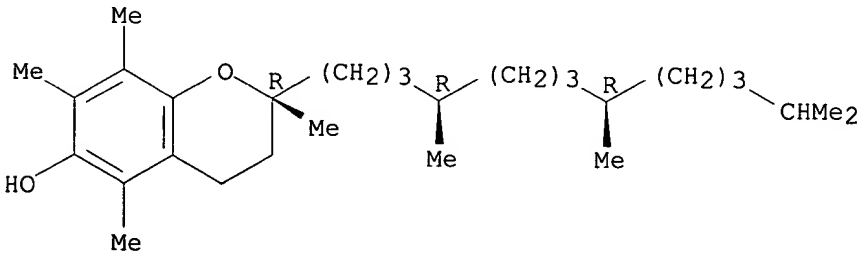
AUTHOR(S): Stocker, Roland; Bowry, Vincent W.; Frei, Balz
CORPORATE SOURCE: Heart Res. Inst., Camperdown, 2050, Australia
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1991), 88(5), 1646-50
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The temporal disappearance of natural **antioxidants** assocd. with **human** low-d. lipoprotein (**LDL**) in relation to the appearance of various classes of lipid hydroperoxides was investigated under three types of oxidizing conditions. Freshly isolated **LDL** from plasma of healthy subjects was free of detectable amts. of lipid hydroperoxides as measured by HPLC postcolumn chemiluminescence detection. Exposure of such **LDL** to a mild, const. flux of aq. peroxyl radicals led to rapid and complete oxidn. of ubiquinol-10, followed by slower partial depletion of lycopene, .beta.-carotene, and .alpha.-tocopherol. After an initial lag period of complete inhibition of detectable lipid peroxidn., formation of hydroperoxides of cholesterol esters, triglycerides, and phospholipids was obsd. The onset of detectable lipid peroxidn. corresponded closely with the completion of ubiquinol-10 consumption. However, small amts. of ascorbate, present as a contaminant in the **LDL** prepn., rather than ubiquinol-10 itself were responsible for the initial lag period. Thus, complete consumption of ubiquinol-10 was preceded by that of ascorbate, and exposure of ascorbate-free **LDL** to aq. peroxyl radicals resulted in immediate formation of detectable amts. of lipid hydroperoxides. The rate of radical-mediated formation of lipid hydroperoxides in ascorbate-free **LDL** was low as long as ubiquinol-10 was present, but increased rapidly after its consumption, even though more than 80% and 95% of endogenous carotenoids and .alpha.-tocopherol, resp., were still present. Qual. similar results were obtained when peroxyl radicals were generated within **LDL** or when the lipoprotein was exposed to **oxidants** produced by activated **human** polymorphonuclear leukocytes. **LDL** oxidn. was reduced significantly by supplementing the lipoprotein prepn. with physiol. amts. of either ascorbate or ubiquinol-10. The data show that ubuquinol-10 is much more efficient in inhibiting **LDL** oxidn. than either lycopene, .beta.-carotene, or .alpha.-tocopherol.

IT **59-02-9**, .alpha.-Tocopherol
RL: BIOL (Biological study)
(low-d. lipoprotein peroxidn. **prevention** by, **atherosclerosis prevention** in relation to, in humans)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 35 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:22762 CAPLUS
DOCUMENT NUMBER: 114:22762
TITLE: Physiologic levels of ascorbate inhibit the **oxidative** modification of low density

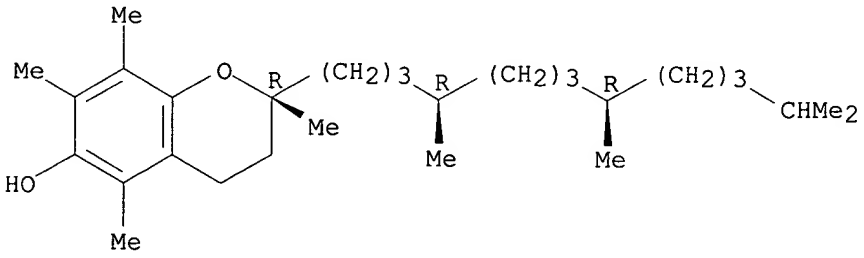
lipoprotein
AUTHOR(S): Jialal, Ishwarlal; Vega, Gloria Lena; Grundy, Scott M.
CORPORATE SOURCE: Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235, USA
SOURCE: Atherosclerosis (Shannon, Irel.) (1990), 82(3), 185-91
CODEN: ATHSBL; ISSN: 0021-9150
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Oxidatively** modified low-d. lipoprotein (**LDL**) could contribute to the **atherosclerotic** process by its cytotoxic effect, uptake by the scavenger receptor and influence on monocyte and macrophage motility. The aim of the present study was to examine the effect of physiol. levels of .alpha.-tocopherol and ascorbate on Cu2+-induced **oxidative** modification of **LDL**. Whereas .alpha.-tocopherol had an inhibitory effect on the **oxidative** modification of **LDL** only for 5 h, as evidenced by the electrophoretic mobility and lipid peroxide content, ascorbate inhibited the **oxidative** modification of **LDL** for both 5 and 24 h. By inhibiting the **oxidative** modification of **LDL**, ascorbate **prevented** the uptake an degrdn. of **oxidatively** modified **LDL** by the scavenger-receptor mechanism of cultured **human** monocyte derived macrophages. It thus appears that in this cell-free system (2.5 .mu.M Cu2+), ascorbate is a more potent **antioxidant** than .alpha.-tocopherol. These findings indicate that ascorbate in physiol. concns. should inhibit the **oxidative** modification of **LDl** in vivo.

IT **59-02-9**, .alpha.-Tocopherol
RL: BIOL (Biological study)
(**oxidative** modification of low-d. lipoproteins response to, in **human** macrophages)

RN 59-02-9 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 36 OF 60 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:549901 CAPLUS
DOCUMENT NUMBER: 113:149901
TITLE: Endogenous **antioxidants** and lipoprotein **oxidation**
AUTHOR(S): Esterbauer, Hermann; Dieber-Rotheneder, Martina; Waeg, Georg; Puhl, Herbert; Tatzber, Franz
CORPORATE SOURCE: Inst. Biochem., Univ. Graz, Graz, A-8010, Austria
SOURCE: Biochem. Soc. Trans. (1990), 18(6), 1059-61
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Data from biochem., clin., and epidemiol. studies suggest that **oxidatively** modified low-d. lipoprotein (**LDL**) is atherogenic and that **preventing LDL** oxidn. by **antioxidants** could diminish the risk of ischemic heart disease.

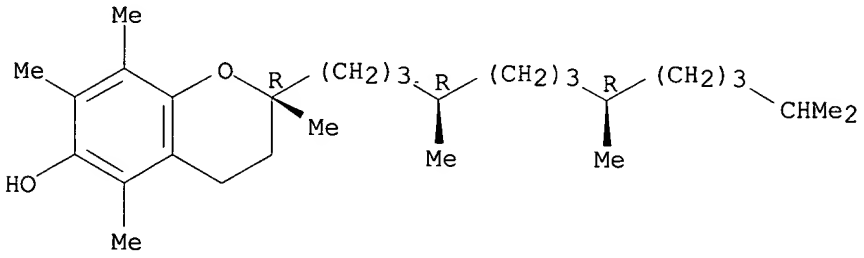
This study investigated Cu2+-stimulated oxidn. of **LDL** in **human** blood samples with emphasis on endogenous **antioxidants** contained in **LDL** and on the length of the lag phase during which **LDL** is protected against oxidn. On a molar basis, by far the major **antioxidant** in **LDL** was found to be .alpha.-tocopherol.

IT **59-02-9**, .alpha.-Tocopherol
RL: BIOL (Biological study)
(as endogenous **antioxidant**, oxidn. of low-d. lipoproteins of humans responses to, **atherosclerosis** in relation to)

RN 59-02-9 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L22 ANSWER 37 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:194962 BIOSIS
DOCUMENT NUMBER: PREV200100194962
TITLE: Protective effect of fluvastatin on degradation of apolipoprotein B by a radical reaction in **human** plasma.
AUTHOR(S): Aoki, Shoichi (1); Ikeda, Kazumi; Yamamura, Michio; Kojo, Shosuke
CORPORATE SOURCE: (1) Tanabe R and D Service, Co., Ltd., 3-16-89 Kashima, Yodogawa-ku, Osaka, 532-8505: s-aoki@tanabe.co.jp Japan
SOURCE: Biological & Pharmaceutical Bulletin, (February, 2001) Vol. 24, No. 2, pp. 123-126. print.
ISSN: 0918-6158.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Fluvastatin, which is a synthetic 3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA) reductase inhibitor, its metabolites (M2, M3 and M4) and trolox all inhibited the decrease of apolipoprotein B-100 (apoB) and alpha-tocopherol in a radical reaction of **human** plasma initiated by Cu2+. The concentrations of fluvastatin, M2, M3, M4 and trolox for 50% inhibition (IC50) of apoB fragmentation were 405, 8.55, 1.75, 305, and 43.4 muM, respectively. The IC50 value of pravastatin, which is another HMG-CoA reductase inhibitor, was 2880 muM, showing that pravastatin is not an effective **antioxidant**. Although fluvastatin, its metabolites and trolox inhibited the decrease of alpha-tocopherol in a similar manner to that of apoB, pravastatin did not significantly inhibit the decrease of alpha-tocopherol. Since **oxidation** of low density lipopotein (**LDL**) is an important step in the initiation and progression of **atherosclerosis**, fluvastatin may reduce the risk of **atherosclerosis** not only by lowering plasma cholesterol but also by protecting **LDL** from **oxidation**.

L22 ANSWER 38 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:146984 BIOSIS
DOCUMENT NUMBER: PREV200100146984

TITLE: Vitamin E and **atherosclerosis**: Beyond **prevention** of **LDL oxidation**.
AUTHOR(S): Meydani, Mohsen (1)
CORPORATE SOURCE: (1) Vascular Biology Laboratory, Jean Mayer U.S. Department of Agriculture, Human Nutrition Research Center on Aging at Tufts University, Boston, MA, 02111 USA
SOURCE: Journal of Nutrition, (February, 2001) Vol. 131, No. 2, pp. 366S-368S. print.
ISSN: 0022-3166.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Atherosclerosis** is a chronic inflammatory disease of the arterial wall. Observational and experimental studies indicate that dietary vitamin E supplementation is associated with reduced risk of **atherosclerosis**. Evidence indicates that vitamin E, in addition to inhibition of **oxidative** modification of **LDL**, may inhibit atherogenesis through several other mechanisms at the molecular and cellular levels, which also include its **nonantioxidant** functions.

L22 ANSWER 39 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:145480 BIOSIS
DOCUMENT NUMBER: PREV200100145480
TITLE: Ex vivo low-density lipoprotein oxidizability and in vivo lipid **peroxidation** in patients on CAPD.
AUTHOR(S): Roob, Johannes M.; Rabold, Thomas; Hayn, Marianne; Khoschsorur, Gholamali; Resch, Ulrike; Holzer, Herwig; Winklhofer-Roob, Brigitte M. (1)
CORPORATE SOURCE: (1) Institute of Molecular Biology, Biochemistry and Microbiology, Karl-Franzens University, Schubertstrasse 1, A-8010, Graz: brigitte.winklhoferroob@kfunigraz.ac.at Austria
SOURCE: Kidney International, (February, 2001) Vol. 59, No. Supplement 78, pp. S.128-S.136. print.
ISSN: 0085-2538.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background. Chronic renal failure is associated with accelerated **atherosclerosis** and a high incidence of cardiovascular disease. **Oxidative** modification of low-density lipoprotein (**LDL**) is considered a key event in atherogenesis. Methods. We studied the ex vivo oxidizability of **LDL** exposed to Cu2+ ions (lag time, rate of propagation, maximum conjugated diene formation) and its relationship with **LDL** density, fatty acids, and **antioxidants**, along with plasma malondialdehyde (MDA) and autoantibodies against Cu2+-, MDA-, and hypochlorous acid-modified **LDL** and plasma **antioxidants** in 17 continuous ambulatory peritoneal dialysis (CAPD) patients and 21 healthy control subjects. Results. **LDL** alpha- and gamma-tocopherol and total polyunsaturated fatty acid (PUFA) concentrations were significantly higher in the CAPD patients. **LDL** density was shifted to small, dense **LDL**. **LDL** oxidizability was comparable to that of healthy subjects. Lag time correlated positively with **LDL** alpha-tocopherol and inversely with both total PUFA concentrations and density; the rate of **oxidation** and **LDL** density correlated positively with total PUFA and total fatty acid concentrations, respectively. Ratios of autoantibody titers against oxidized to native **LDL** did not differ between the two groups. While plasma alpha- and gamma-tocopherol concentrations and tocopherol to cholesterol ratios were significantly higher, vitamin C concentrations were very low in the CAPD patients. MDA concentrations were 1.7 times higher than in healthy subjects. Conclusions. (1) Ex vivo **LDL** oxidizability is normal in CAPD

patients as a result of efficient protection by **LDL**-associated lipophilic **antioxidants**, although the **LDL** composition is altered toward high oxidizability; and (2) the plasma **antioxidant** screen is insufficient due to impaired vitamin C status.

L22 ANSWER 40 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:523303 BIOSIS
DOCUMENT NUMBER: PREV200000523303
TITLE: Evidence for **oxidative** activation of c-Myc-dependent nuclear signaling in **human** coronary smooth muscle cells and in early lesions of Watanabe heritable hyperlipidemic rabbits: Protective effects of vitamin E.
AUTHOR(S): de Nigris, Filomena; Youssef, Tammam; Ciafre, SilviaAnna; Franconi, Flavia; Anania, Vittorio; Condorelli, GianLuigi; Palinski, Wulf; Napoli, Claudio (1)
CORPORATE SOURCE: (1) Medicine, Via B. Falcomata' 5, 80128, Naples Italy
SOURCE: Circulation, (October 24, 2000) Vol. 102, No. 17, pp. 2111-2117. print.
ISSN: 0009-7322.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background-Oxidized **LDL** (oxLDL) promotes atherogenesis, and **antioxidants** reduce lesions in experimental models. OxLDL-mediated effets on c-Myc are poorly characterized, and those on c-Myc nuclear pathways are completely unknown. c-Myc stimulates smooth muscle cell (SMC) proliferation and could be involved in **atherosclerosis**. We investigated the early effects of oxLDL and alpha-tocopherol on c-Myc, its binding partner Max, and the carboxy-terminal domain-binding factors activator protein-2 and elongation 2 factor in **human** coronary SMCs. We also investigated whether 9-week **treatment** of Watanabe heritable hyperlipidemic (WHHL) rabbits with diet-enriched X-tocopherol reduces c-Myc expression and oxLDL in the left coronary artery. Methods and Results-OxLDL enhanced c-Myc/Max expression and transcription by cotransfection assay and the nuclear activities of E2F and activator protein-2 by binding shift and supershift in coronary SMCs. alpha-Tocopherol significantly reduced these molecular events. Furthermore, alpha-tocopherol reduced early lesions, SMC density, and the immunohistochemical presence of c-Myc, which colocalized with oxLDL/foam cells in the coronaries of WHHL rabbits. Conclusions-We provide the first evidence that oxLDL and alpha-tocopherol may incluence c-Myc activation and several c-Myc-dependent signaling pathways in **human** coronary SMCs. The observation that in vivo, an **antioxidant** reduces both c-Myc and oxLDL in early coronary lesions of rabbits is consistent, but does not prove, the hypothesis that c-Myc-dependent factors activated by **oxidative** processes contribute to atherogenesis and coronary heart disease.

L22 ANSWER 41 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:368278 BIOSIS
DOCUMENT NUMBER: PREV200000368278
TITLE: Vitamin E reduces the uptake of oxidized **LDL** by inhibiting CD36 scavenger receptor expression in cultured aortic smooth muscle cells.
AUTHOR(S): Ricciarelli, Roberta; Zingg, Jean-Marc; Azzi, Angelo (1)
CORPORATE SOURCE: (1) Institut fur Biochemie und Molekularbiologie, Universitat Bern, Buhlstrasse 28, Bern, 3012 Switzerland
SOURCE: Circulation, (July 4, 2000) Vol. 102, No. 1, pp. 82-87. print.
ISSN: 0009-7322.
DOCUMENT TYPE: Article
LANGUAGE: English

SUMMARY LANGUAGE: English
AB Background-Vitamin E is well known as an **antioxidant**, and numerous studies suggest that it has a **preventive** role in **atherosclerosis**, although the mechanism of action still remains unclear. Methods and Results-The original aim of this study was to establish whether alpha-tocopherol (the most active form of vitamin E) acts at the earliest events on the cascade of **atherosclerosis** progression, that of oxidized **LDL** (oxLDL) uptake and foam-cell formation. We show here that the CD36 scavenger receptor (a specific receptor for oxLDL) is expressed in cultured **human** aortic smooth muscle cells (SMCs). **Treatment** of SMCs and HL-60 macrophages with alpha-tocopherol (50 mumol/L, a physiological concentration) downregulates CD36 expression by reducing its promoter activity. Furthermore, we find that alpha-tocopherol **treatment** of SMCs leads to a reduction of oxLDL uptake. Conclusions-This study indicates that CD36 is expressed in cultured **human** SMCs. In these cells, CD36 transports oxLDL into the cytosol. alpha-Tocopherol inhibits oxLDL uptake by a mechanism involving downregulation of CD36 mRNA and protein expression. Therefore, the beneficial effect of alpha-tocopherol against **atherosclerosis** can be explained, at least in part, by its effect of lowering the uptake of oxidized lipoproteins, with consequent reduction of foam cell formation.

L22 ANSWER 42 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:9417 BIOSIS
DOCUMENT NUMBER: PREV200000009417
TITLE: **Antioxidant** supplementation effects on low-density lipoprotein **oxidation** for individuals with type 2 diabetes mellitus.
AUTHOR(S): Anderson, James W. (1); Gowri, Maya S.; Turner, Jan; Nichols, Laura; Diwadkar, Veda A.; Chow, Ching K.; Oeltgen, Peter R.
CORPORATE SOURCE: (1) Medical Service, 111C, VA Medical Center, 2250 Leestown Road, Lexington, KY, 40511 USA
SOURCE: Journal of the American College of Nutrition, (Oct., 1999) Vol. 18, No. 5, pp. 451-461.
ISSN: 0731-5724.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective: This study compared susceptibility to **oxidation** of low-density lipoproteins (**LDL**) of non-diabetic and diabetic (Type 2) men and examined the response of diabetic men to **antioxidant** supplementation (alpha-tocopherol, beta-carotene and ascorbate). Research Design and Methods: Twenty adult non-diabetic and 20 diabetic men were recruited. **Oxidation** of **LDL** was assessed by four different assay systems, and the extent of **oxidation** was assessed by four different measurements. Diabetic men received eight weeks of placebo ("baseline"), twelve weeks of **antioxidant** supplements ("**treated**") and eight weeks of placebo ("post-**treatment**"). Supplements provided 24 mg of beta-carotene, 1000 mg of ascorbate and 800 IU of alpha-tocopherol daily. Results: With Cu **oxidation** at 37degreeC, thiobarbituric reactive substances (TBARS) formation was significantly higher ($p=0.032$) and loss of free amine groups was significantly greater ($p=0.013$) in the **LDL** from diabetic subjects than controls. **Antioxidant** supplementat ion of diabetic subjects significantly decreased all parameters of **LDL oxidation** with Cu at 30degreeC and 37degreeC. At 30degreeC the lag phase increased from 55 to 129 minutes ($p<0.0001$); conjugated diene formation decreased from 1.23 to 0.62 OD units ($p<0.0001$); TBARS formation decreased from 78 to 33 nmoles MDA/mg **LDL** protein ($p<0.0001$); and free amine loss decreased from 41 to 12% ($p<0.0001$). With Cu **oxidation** at 37degreeC, similar changes occurred. Conclusions: These studies indicate that the **LDL** from

diabetic subjects are more susceptible to **oxidation** than **LDL** from non-diabetic subjects. Supplementation of diabetic subjects with **antioxidant** vitamins significantly decreases susceptibility of **LDL** to **oxidation** by Cu. These studies are consistent with epidemiological and intervention studies suggesting that **antioxidant** vitamin use significantly decreases risk for coronary heart disease.

L22 ANSWER 43 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:357959 BIOSIS
DOCUMENT NUMBER: PREV199800357959
TITLE: **LDL oxidation**: Therapeutic perspectives.
AUTHOR(S): Heller, Francis R. (1); Descamps, Olivier; Hondekijn, Jean-Claude
CORPORATE SOURCE: (1) Dep. Internal Med., Hopital De Jolimont, 7100 Haine-Saint-Paul Belgium
SOURCE: Atherosclerosis, (April, 1998) Vol. 137, No. SUPPL., pp. S25-S31.
ISSN: 0021-9150.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB The **peroxidation** step of lipid transformation is considered to be essential in the pathogenesis of **atherosclerosis**. Although data concerning the mechanisms by which lipid **peroxidation** occurs in vivo are scarce, several lines of evidence suggest that some endogenous and exogenous compounds with **antioxidant** activity could have some beneficial effects in the **prevention** of **atherosclerosis**. Ascorbic acid (vitamin C) and alpha-tocopherol (vitamin E) act as the most important hydrophilic and lipophilic **antioxidants**, respectively in vivo. Accordingly, animal and **human** studies suggest that these compounds may have some **preventive** effect against the development of clinical coronary heart disease. Many plant phenols and flavonoids may be important dietary **antioxidants** and it has been speculated that these compounds in red wine or in the Mediterranean diet could explain the 'French paradox'. Several studies show that **antioxidants** such as probucol and butylated hydroxytoluene can inhibit development of **atherosclerotic** lesions in Watanabe and cholesterol-fed rabbits. Some drugs such as beta-blockers, calcium antagonists, hypolipidemic drugs .... appear to have at least in vitro **antioxidant** effects but the clinical relevance of these properties remains unknown. Moreover, some interventions aimed to decrease the **LDL-oxidative** susceptibility have not been shown to attenuate atherogenesis when cholesterol levels remain markedly elevated.

L22 ANSWER 44 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:34742 BIOSIS
DOCUMENT NUMBER: PREV199800034742
TITLE: **Oxidation** of free fatty acids in low density lipoprotein by 15-lipoxygenase stimulates nonenzymic, alpha-tocopherol-mediated **peroxidation** of cholesteryl esters.
AUTHOR(S): Upston, Joanne M.; Neuzil, Jiri; Witting, Paul K.; Alleva, Renata; Stocker, Roland (1)
CORPORATE SOURCE: (1) Biochem. Unit, Heart Res. Inst., 145 Missenden Rd., Camperdown, NSW 2050 Australia
SOURCE: Journal of Biological Chemistry, (Nov. 28, 1997) Vol. 272, No. 48, pp. 30067-30074.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB 15-Lipoxygenase has been implicated in the in vivo **oxidation** of low density lipoprotein (**LDL**) a process thought to be important

in the origin and/or progression of **human** atherogenesis. We have suggested previously that **oxidation** of **LDL**'s cholesteryl esters (CE) and phospholipids by soybean (SLO) or **human** recombinant 15-lipoxygenase (rhLO) can be ascribed largely to alpha-tocopherol (alpha-TOH)-mediated **peroxidation** (TMP). In this study we demonstrate that addition to **LDL** of unesterified linoleate (18:2), other free fatty acid (FFA) substrates, or phospholipase A2 (PLA2) significantly enhanced the accumulation of CE hydro(pero)xides (CEO(O)H) induced by rhLO, whereas the corresponding CE and nonsubstrate FFA were without effect. The enhanced CE-O(O)H accumulation showed a dependence on the concentration of free 18:2 in **LDL**. In contrast, addition of 18:2 had little effect on **LDL** **oxidation** induced by aqueous peroxyl radicals or Cu2+ ions. Analyses of the regio- and stereoisomers of oxidized 18:2 in SLO-**treated** native **LDL** demonstrated that the small amounts of 18:2 associated with the lipoprotein were oxidized enzymically and within minutes, whereas cholesteryl linoleate (Ch18:2) was oxidized nonenzymically and continuously over hours. alpha-Tocopheroxyl radical (alpha-TO.) formed in **LDL** exposed to SLO was enhanced by addition of 18:2 or PLA2. With rhLO and 18:2-supplemented **LDL**, **oxidation** of 18:2 was entirely enzymic, whereas that of Ch18:2 was largely, though not completely, nonenzymic. The small extent of enzymic Ch18:2 **oxidation** increased with increasing enzyme to **LDL** ratios. Ascorbate and the reduced form of coenzyme Q, ubiquinol-10, which are both capable of reducing alpha-TO. and thereby **preventing** TMP, inhibited nonenzymic Ch18:2 **oxidation** induced by rhLO. Trolox and ascorbyl palmitate, which also inhibit TMP, ameliorated both enzymic and nonenzymic **oxidation** of **LDL**'s lipids, whereas probucol, a radical scavenger not capable of **preventing** TMP, was ineffective. These results demonstrate that rhLO-induced **oxidation** of CE is largely nonenzymic and increases with **LDL**'s content of FFA substrates. We propose that conditions which increase **LDL**'s FFA content, such as the presence of lipases, increase 15-LO-induced **LDL** lipid **peroxidation** and that this process requires only an initial, transient enzymic activity.

L22 ANSWER 45 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:483498 BIOSIS
DOCUMENT NUMBER: PREV199799782701
TITLE: Moderate beer consumption and positive biochemical changes in patients with coronary **atherosclerosis**.
AUTHOR(S): Gorinstein, S. (1); Zemser, M.; Berliner, M.; Goldstein, R.; Libman, I.; Trakhtnberg, S.; Caspi, A.
CORPORATE SOURCE: (1) Dep. Pharmaceutical Chemistry Sch. Pharmacy, Hebrew Univ. Jerusalem, Jerusalem 91120 Israel
SOURCE: Journal of Internal Medicine, (1997) Vol. 242, No. 3, pp. 219-224.
ISSN: 0954-6820.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Objectives: The aim of this study was to evaluate the influence of moderate beer consumption on lipid metabolism and **antioxidant** activity in patients (pts) with coronary artery disease (CAD). Subjects: Forty-eight male pts with CAD not alcohol beverages consumers were randomly divided into experimental (EG) and control (CG) groups, 24 pts each. Setting: Rehovot University Hospital, Israel. Intervention: Every patient of the EG during a period of 30 consecutive days consumed 330 ml of Maccabee beer (gt 20 g of alcohol). The pts of the CG did not consume alcohol during the trial period. Methods: A wide range of tests including total cholesterol, **LDL**-C, HDL-C, total tocopherol and alpha-tocopherol. Results. Only in the pts of the EG were found a tendency to an increase of the level of HDL-C and a statistically significant rise in the level of total tocopherol (P lt 0.025) and alpha-tocopherol (P lt 0.025). Conclusions. Even a short period of moderate beer consumption

leads to some favourable biochemical changes in blood of pts with CAD which are widely regarded as indicators of CAD **prevention**.

L22 ANSWER 46 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:241349 BIOSIS
DOCUMENT NUMBER: PREV199799540552
TITLE: Alpha tocopherol level and autoantibodies to CU-2+-oxidized lipoproteins in healthy adults.
AUTHOR(S): Bui, Minh N.; Bui, Chau; Moutsatsos, George; Echard, Bob; Caulfield, Mike; Rackley, Charles E.
CORPORATE SOURCE: Dep. Med., Georgetown Univ., Washington, DC USA
SOURCE: Journal of Investigative Medicine, (1997) Vol. 45, No. 3, pp. 218A.
Meeting Info.: Annual Meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American Federation for Medical Research: Biomedicine '97 Medical Research from Bench to Bedside Washington, D.C., USA April 25-27, 1997
ISSN: 1081-5589.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L22 ANSWER 47 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:571757 BIOSIS
DOCUMENT NUMBER: PREV199799286438
TITLE: Oxidized low-density lipoprotein and **atherosclerosis**.
AUTHOR(S): Devaraj, S.; Jialal, I. (1)
CORPORATE SOURCE: (1) Dep. Pathol. Intern. Med., University Texas Southwestern Medical Cent., 5323 Harry Hines Blvd., Dallas, TX 75235-9072 USA
SOURCE: International Journal of Clinical & Laboratory Research, (1996) Vol. 26, No. 3, pp. 178-184.
ISSN: 0940-5437.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB **Atherosclerosis** is the leading cause of morbidity and mortality in western society. The most important risk factors for **atherosclerosis** include smoking, hypertension, dyslipidemia, diabetes and a family history of premature **atherosclerosis**. Several studies indicate that an increased plasma low density lipoprotein (**LDL**) cholesterol constitutes a major risk factor for **atherosclerosis**. Many data support a proatherogenic role for oxidized **LDL** and its in vivo existence. The **oxidative** susceptibility of **LDL** is increased with established cardiovascular risk factors, such as diabetes, smoking and dyslipidemia. Supplementation with **antioxidants** such as ascorbate and alpha-tocopherol can decrease **LDL oxidation** as well as cardiovascular mortality and thus shows promise in the **prevention** of **atherosclerosis**.

L22 ANSWER 48 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:467606 BIOSIS
DOCUMENT NUMBER: PREV199699189962
TITLE: What dose of vitamin E is required to reduce susceptibility of **LDL** to **oxidation**.
AUTHOR(S): Simons, L. A. (1); Von Konigsmark, M.; Balasubramaniam, S.
CORPORATE SOURCE: (1) Lipid Res. Dep., St. Vincent's Hosp., Darlinghurst, NSW 2010 Australia
SOURCE: Australian and New Zealand Journal of Medicine, (1996) Vol. 26, No. 4, pp. 496-503.
ISSN: 0004-8291.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Background: **Oxidative** modification of low density lipoprotein (**LDL**) may play a role in the pathogenesis of **atherosclerosis**. Ingestion of vitamin E in high dosage has been shown to reduce the susceptibility of **LDL** to copper-induced **oxidation**, as assessed ex vivo. Aim: To determine a minimum dose of supplementary vitamin E which will significantly reduce the susceptibility of **LDL** to **oxidation**. Methods: A single centre, double-blind, parallel placebo-controlled trial. Healthy volunteers (total n=42) were randomised to receive placebo, 500, 1000 or 1500 IU/day of vitamin E (D-alpha-tocopherol) for a period of six weeks. Primary outcomes were change in lag time or **oxidation** rate to copper-induced **LDL oxidation**. Secondary outcomes were changes in plasma vitamin E levels and clinical tolerance. Results: Lag time to **LDL oxidation** was significantly prolonged and **oxidation** rate significantly slowed at all dose levels of vitamin E, indicating a threshold effect from 500 IU/day. Compared to placebo, the median prolongation in lag time on 500 IU/day was 26%, on 1000 IU/day 24% and on 1500 IU/day 35%. The corresponding slowing in **oxidation** rates was 14%, 19% and 25% respectively. The per cent change in plasma vitamin E concentration was highly correlated with the change in lag time (r=0.61, p lt 0.001) and **oxidation** rate (r=-0.55,p lt 0.001). Vitamin E was generally well tolerated. Conclusions: Vitamin E in a dose of 500 IU/day will significantly reduce the susceptibility of **LDL** to **oxidation**. Whether or not this **treatment** will consistently reduce the future incidence of coronary artery disease will only be answered by further clinical trials.

L22 ANSWER 49 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:279290 BIOSIS
DOCUMENT NUMBER: PREV199699001646
TITLE: Alpha-Tocopherol as a reductant for Cu(II) in **human** lipoproteins: Triggering role in the initiation of lipoprotein **oxidation**.
AUTHOR(S): Kontush, Anatol (1); Meyer, Stefanie; Finckh, Barbara; Kohlschuetter, Alfried; Beisiegel, Ulrike
CORPORATE SOURCE: (1) Biochemisches Labor, Medizinische Kern-und Poliklinik, Universitaeskrankenhaus Eppendorf, Martinstrasse 52, 20246 Hamburg Germany
SOURCE: Journal of Biological Chemistry, (1996) Vol. 271, No. 19, pp. 11106-11112.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Initiation of lipid **peroxidation** by Cu(II) requires reduction of Cu(II) to Cu(I) as a first step. It is unclear, however, whether this reaction occurs in the course of lipoprotein **oxidation**. It is also unknown which reductant, if any, can drive the reduction of Cu(II) in this case. We found that Cu(II) was rapidly reduced to Cu(I) by all major **human** lipoproteins (high, low, and very low density lipoproteins (HDL, **LDL**, and VLDL), and chylomicrons). Cu(II)-reducing activity was associated with a lipid moiety of the lipoproteins. The rates of Cu(II) reduction by different lipoproteins were similar when the lipoproteins were adjusted to similar alpha-tocopherol concentrations. Enriching lipoproteins with alpha-tocopherol considerably increased the rate of Cu(II) reduction. Cu(II) reduction by alpha-tocopherol-deficient **LDL** isolated from a patient with familial inherited vitamin E deficiency was found to occur much slower in comparison with **LDL** isolated from a donor with a normal plasma level of alpha-tocopherol. Initial rate of Cu(II) reduction by alpha-tocopherol-deficient **LDL** was found to be zero. Enriching **LDL** with ubiquinol-10 to concentrations close to those of alpha-tocopherol did not influence the reaction rate. When **LDL** was **treated** with ebselen to eliminate preformed lipid hydroperoxides, the reaction rate was also not changed significantly. Cu(II) reduction was accompanied by a consumption

of lipoprotein alpha-tocopherol and accumulation of conjugated dienes in the samples. Increasing alpha-tocopherol content in lipoproteins slightly decreased the rate of conjugated diene accumulation in **LDL** and HDL and considerably increased it in VLDL. The results suggest that alpha-tocopherol plays a triggering role in the lipoprotein **oxidation** by Cu(II), providing its initial step as follows: alpha-TocH + Cu(II) fwdarw alpha-Toc. + Cu(I) + H+. This reaction appears to diminish or totally eliminate the **antioxidative** activity of alpha-tocopherol in the course of lipoprotein **oxidation**.

L22 ANSWER 50 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:266503 BIOSIS
DOCUMENT NUMBER: PREV199698822632
TITLE: Effect of dietary fish oil supplementation on **peroxidation** of serum lipids in patients with non-insulin dependent diabetes mellitus.
AUTHOR(S): McGrath, Lawrence T. (1); Brennan, Geraldine M.; Donnelly, James P.; Johnston, G. Dennis; Hayes, J. Randal; McVeigh, Gary E.
CORPORATE SOURCE: (1) Dep. Therapeutics Pharmacology, Queen's Univ. Belfast, 97 Lisburn Road, Belfast BT9 7BL UK
SOURCE: Atherosclerosis, (1996) Vol. 121, No. 2, pp. 275-283. ISSN: 0021-9150.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Lipid **peroxidation** may be important in the development of cardiovascular disease, a common cause of mortality and morbidity in non-insulin dependent diabetes mellitus (NIDDM). We assessed the degree of lipid **peroxidation** by measuring plasma malondialdehyde, as thiobarbituric acid reacting substances (TBARS), in 23 non-insulin dependent diabetic patients. Plasma levels of lipid standardised alpha-tocopherol (vitamin E), lipid content of whole plasma and lipoprotein fractions, glycosylated haemoglobin, glycosylated low density lipoprotein (**LDL**) and fasting blood glucose were also measured. On completion of the baseline studies patients randomly received either fish oil or matching olive oil capsules in a double blind crossover fashion for 6 weeks followed by a 6 week washout period and a final 6 week **treatment** phase. Studies, identical to the initial baseline studies, were performed at the end of the active **treatment** periods at 6 and 18 weeks. **Treatment** with olive oil did not change levels of TBARS, vitamin E or indices of glycaemic control compared with baseline. Total cholesterol and triglyceride (TG) content of plasma and lipoprotein fractions were not significantly altered. **Treatment** with fish oil resulted in elevation of TBARS (P lt 0.001) and reduction of vitamin E (P lt 0.01) compared with baseline and olive oil **treatment**. Plasma cholesterol was unchanged. A reduction in plasma TG compared with baseline occurred but failed to reach significance (P = 0.07). Changes in apo B containing lipoproteins induced by fish oil failed to reach significance. No significant changes were observed in the concentration or composition of high density lipoprotein (HDL). Fish oil **treatment** showed no change in glycaemic control as assessed by glycosylated haemoglobin and **LDL** although a rise in fasting blood glucose just failed to reach significance (P = 0.06). Lipid **peroxidation** in NIDDM can be exacerbated by dietary fish oil. This potentially adverse reaction may limit the therapeutic use of fish oils in such patients.

L22 ANSWER 51 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:103326 BIOSIS
DOCUMENT NUMBER: PREV199698675461
TITLE: Plasmalogen phospholipids in plasma lipoproteins of normolipidemic donors and patients with hypercholesterolemia **treated** by **LDL** apheresis.

AUTHOR(S): Braeutigam, Carola; Engelmann, Bernd (1); Reiss, Daniela; Reinhardt, Ulrike; Thiery, Joachim; Richter, Werner O.; Brosche, Thorolf
CORPORATE SOURCE: (1) Physiol. Inst., Univ. Muenchen, Pettenkoferstr. 12, D-80336 Muenchen Germany
SOURCE: Atherosclerosis, (1996) Vol. 119, No. 1, pp. 77-88. ISSN: 0021-9150.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Recent evidence indicates that plasmalogen phospholipids are particularly sensitive to **oxidation** and may possess **antioxidative** properties. Approximately 4.4%-5.5% of phosphatidylcholine (PC), and 53%-60% of phosphatidylethanolamine (PE) consisted of the plasmalogen phospholipids, plasmenylcholine and plasmenylethanolamine, respectively, in whole plasma, low density lipoprotein (**LDL**) and high density lipoprotein (HDL) of 11 normolipidemic donors. Of total plasmalogen phospholipids in plasma, slightly more was associated with **LDL** particles (about 42%) than with HDL (36/o). Plasmalogen phospholipid levels were analyzed in 12 patients with familial hypercholesterolemia (FH) regularly **treated** by **LDL** apheresis, of whom 6 were supplemented with vitamin E (alpha tocopherol, 400 IU/day), the remaining 6 not receiving the **antioxidant**. Before apheresis (pre), total plasmalogen phospholipid levels in plasma and **LDL** (expressed as mu-mol/mmol cholesterol of compartment) decreased as follows: patients receiving vitamin E gt normolipidemia gt patients not receiving vitamin E. In both hypercholesterolemic groups, the contents of plasmalogen phospholipids in whole plasma and **LDL** were 3-5-fold higher than those of vitamin E. Directly after apheresis (post), plasmalogen phospholipid levels in plasma were raised by about 50% in the two hypercholesterolemic groups, mostly due to increases in plasmenylethanolamine levels. Two days after apheresis (48 h post), plasmalogen contents were still elevated in plasma and red blood cell membranes of patients receiving vitamin E, while they had already reached pre-apheresis values in those not supplemented with alpha tocopherol. Molecular species of plasma diacyl phospholipids containing polyunsaturated fatty acids were elevated at pre in patients receiving vitamin E as compared to patients without supplementation. At 48 h post, **LDL** apheresis induced an increase in these molecular species only in patients receiving vitamin E. In conclusion, the contents of plasmalogen phospholipids in plasma lipoproteins are at least three times higher than those of vitamin E. **LDL** apheresis raises the level of plasmalogen phospholipids in plasma, the increase persisting longer in patients supplemented with vitamin E. Supplementation with vitamin E appears to protect plasmalogen phospholipids in plasma lipoproteins against **oxidative** degradation.

L22 ANSWER 52 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:65500 BIOSIS
DOCUMENT NUMBER: PREV199698637635
TITLE: **Coantioxidants** make alpha-tocopherol an efficient **antioxidant** for low-density lipoprotein.
AUTHOR(S): Thomas, Shane R.; Neuzil, Jiri; Mohr, Detlef; Stocker, Roland (1)
CORPORATE SOURCE: (1) Biochem. Group, Heart Research Inst., 145 Missenden Road, Camperdown, Sydney, NSW Australia
SOURCE: American Journal of Clinical Nutrition, (1995) Vol. 62, No. 6 SUPPL., pp. 1357S-1364S. ISSN: 0002-9165.
DOCUMENT TYPE: General Review
LANGUAGE: English

AB The **oxidation** of low-density lipoproteins (LDLs) is now commonly implicated as an important early event in atherogenesis. The resulting interest in **LDL antioxidation** has focused on alpha-tocopherol, the biologically and chemically most active form of

vitamin E and quantitatively the major lipid-soluble **antioxidant** in extracts prepared from **human LDL**. We review advances made in our understanding of the molecular action of alpha-tocopherol in radical-mediated **oxidation** of isolated **human LDL** and how the vitamin's **antioxidant** activity is enhanced or even dependent on the presence of suitable reducing species, which are referred to as **coantioxidants**.

L22 ANSWER 53 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:529483 BIOSIS
DOCUMENT NUMBER: PREV199598543783
TITLE: Dietary **antioxidants** and carotid artery wall thickness: The ARIC study.
AUTHOR(S): Kritchevsksy, Stephen B. (1); Shimakawa, Tomoko; Tell, Grethe S.; Dennis, Barbara; Carpenter, Myra; Eckfeldt, John H.; Peacher-Ryan, Holmes; Heiss, Gerardo
CORPORATE SOURCE: (1) Div. Biostat. Epidemiol., Dep. Preventive Medicine, Univ. Tennessee Memphis, 877 Madison Ave., Memphis, TN 38163 USA
SOURCE: Circulation, (1995) Vol. 92, No. 8, pp. 2142-2150. ISSN: 0009-7322.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Background: Evidence that dietary **antioxidants** may **prevent atherosclerotic** disease is growing. The relationship between the intake of dietary and supplemental vitamin C, alpha-tocopherol, and, provitamin A carotenoids and average carotid artery wall thickness was studied in 6318 female and 4989 male participants 45 to 64 years old in the **Atherosclerosis** Risk in Communities Study. Methods and Results: Intake was assessed by use of a 66-item semiquantitative food-frequency questionnaire. Carotid artery intima-media wall thickness was measured as an indicator of **atherosclerosis** at multiple sites with B-mode ultrasound. Among men and women gt 55 years old who had not recently begun a special diet, there was a significant inverse relationship between vitamin C intake and average artery wall thickness adjusted for age, body mass index, fasting serum glucose, systolic and diastolic blood pressures, HDL and **LDL** cholesterol, total caloric intake, cigarette use, race, and education (test for linear trend across quintiles of intake, P=.019 for women and P=.035 for men). An inverse relationship was also seen between wall thickness and alpha-tocopherol intake but was significant only in women (test for linear trend, P=.033 for women and P=.13 for men). There was a significant inverse association between carotene intake and wall thickness in older men (test for linear trend, P=.015), but the association weakened after adjustment for potential confounders. No significant relationships were seen in participants lt 55 years old. Conclusions: These data provide limited support for the hypothesis that dietary vitamin C and alpha-tocopherol may protect against **atherosclerotic** disease, especially in individuals gt 55 years old.

L22 ANSWER 54 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:498129 BIOSIS
DOCUMENT NUMBER: PREV199598521679
TITLE: The Kuopio **Atherosclerosis Prevention** Study (KAPS): Effect of pravastatin **treatment** on lipids, **oxidation** resistance of lipoproteins, and **atherosclerotic** progression.
AUTHOR(S): Salonen, Riitta (1); Nyyssonen, Kristiina; Porkkala-Sarataho, Elina; Salonen, Jukka T. (1)
CORPORATE SOURCE: (1) Res. Inst. Public Health, Univ. Kuopio, P.O. Box 1627, 70211 Kuopio Finland
SOURCE: American Journal of Cardiology, (1995) Vol. 76, No. 9, pp. 34C-39C. ISSN: 0002-9149.

DOCUMENT TYPE: Article
LANGUAGE: English
AB The Kuopio **Atherosclerosis Prevention** Study is the first population-based, double-blind trial in the primary **prevention** of carotid and femoral **atherosclerosis**. A total of 447 subjects with serum low density lipoprotein (**LDL**) cholesterol levels gtoreq 155 mg/dl (gtoreq 4.0 mmol/liter) and total cholesterol levels lt 290 mg/dl (lt 7.5 mmol/liter) were randomly assigned to receive either pravastatin 40 mg/day or placebo for 3 years. **Atherosclerotic** progression in 424 men was assessed with B-mode ultrasonography. Pravastatin reduced the rate of progression by 45% (95% confidence interval (CI): 16-69%, 7 p = 0.005) in carotid arteries and by 66% (95% CI: 30-90%, p = 0.002) in the common carotid arteries. The **treatment** effect in the carotid arteries was greater in subjects with thick arterial walls at baseline, in smokers, and in subjects with low plasma alpha-tocopherol. Subjects who received pravastatin had a higher **antioxidative** capacity of **LDL**, a longer **oxidation** lag of very low density lipoprotein (VLDL) plus **LDL**, and a reduced **oxidation** rate of VLDL plus **LDL** in vitro. These data establish the antiatherogenic effect of lowering **LDL** cholesterol levels by provastatin therapy in hypercholesterolemic men in a primary **prevention** setting and suggest that part of the antiotherogenic effect of pravastatin may be due to an improvement in the resistance of atherogenic lipoproteins to **oxidation**.

L22 ANSWER 55 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:120398 BIOSIS
DOCUMENT NUMBER: PREV199598134698
TITLE: Vitamin E: Metabolism and role in **atherosclerosis**.
AUTHOR(S): Cogny, A.; Paul, J. L. (1); Soni, T.; Atger, V.; Moatti, N.
CORPORATE SOURCE: (1) Laboratoire de Biochimie, Hopital Broussais, 96 rue Didot, 75014 Paris France
SOURCE: Annales de Biologie Clinique, (1994) Vol. 52, No. 7-8, pp. 515-522.
ISSN: 0003-3898.
DOCUMENT TYPE: General Review
LANGUAGE: French
SUMMARY LANGUAGE: French; English
AB Vitamin E is the term used for eight naturally occurring fat-soluble nutrients. Alpha-tocopherol predominates in many species and has the highest biological activity. Vitamin E is absorbed via the lymphatic pathway and transported in association with CM. Vitamin E is carried in plasma by lipoproteins. It is secreted by the liver in nascent VLDL with a preferential incorporation of alpha-tocopherol. Most of the plasma vitamin E is in **LDL** and in HDL. Vitamin E is exchanged readily between lipoproteins: tocopherol in HDL readily transfers to apolipoprotein B-containing lipoproteins (VLDL, **LDL**), with little return of tocopherol from the apolipoprotein B-containing lipoproteins to HDL. The mechanisms of tissue uptake of vitamin E from the lipoproteins is poorly understood. This uptake may occur during catabolism of triacylglycerol-rich lipoproteins by the activity of lipoprotein lipase, via the **LDL** receptor or by nonreceptor-mediated uptake. Vitamin E may act to **prevent** the initiation/progression of spontaneous **atherosclerosis**. This concept is based on in-vitro data: vitamin E influences the responses of cells (vascular endothelial cells, leukocytes, vascular smooth muscle cells) and the modification of lipoproteins (especially **LDL**) which, at least in principle, could contribute to the initiation/progression of spontaneous **atherosclerosis**. In vivo studies are clearly required to establish the extent and mode of vitamin E's antiatherosclerotic impact and, hence, its therapeutic potential.

L22 ANSWER 56 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:67429 BIOSIS
DOCUMENT NUMBER: PREV199598081729
TITLE: Effects of **antioxidants** and fatty acids on low-density-lipoprotein **oxidation**.
AUTHOR(S): Fuller, Cindy J.; Jialal, Ishwarlal (1)
CORPORATE SOURCE: (1) Cent. Human Nutrition, Univ. Texas Southwestern Med. Cent., 5323 Hary Hines Boulevard, Dallas, TX 75235-9052 USA
SOURCE: American Journal of Clinical Nutrition, (1994) Vol. 60, No. 6 SUPPL., pp. 1010S-1013S.
ISSN: 0002-9165.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Evidence continues to accumulate that implicates the **oxidative** modification of low-density lipoprotein (**LDL**) in the pathogenesis of **atherosclerosis**. Numerous studies have indicated the existence of oxidized **LDL** in vivo. Supplementation of animals and humans with **antioxidants** such as (gamma-tocopherol have shown promise in reducing the extent of **LDL** **oxidation**. However, another possible means of **preventing** **LDL** **oxidative** modification may be by reducing the amount of oxidizable polyunsaturated fatty acids in the **LDL** particle. Monounsaturated fatty acids have been shown to decrease the susceptibility of **LDL** **oxidation** in **human** studies. It remains to be seen whether saturated fatty acids can do the same. Stearic acid, found in cocoa butter, would be an ideal saturated fatty acid to test because it has a neutral effect on the plasma lipid profile.

L22 ANSWER 57 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:65268 BIOSIS
DOCUMENT NUMBER: PREV199598079568
TITLE: Involvement of Preexisting Lipid Hydroperoxides in Cu-2+-Stimulated **Oxidation** of Low-Density Lipoprotein.
AUTHOR(S): Thomas, James P.; Kalyanaraman, B.; Girotti, Albert W. (1)
CORPORATE SOURCE: (1) Dep. Biochem., Med. Coll. Wisconsin, Milwaukee, WI 53226 USA
SOURCE: Archives of Biochemistry and Biophysics, (1994) Vol. 315, No. 2, pp. 244-254.
ISSN: 0003-9861.
DOCUMENT TYPE: Article
LANGUAGE: English
AB **Oxidative** modification of **human** low-density lipoprotein (**LDL**) is thought to play an important role in the development of **atherosclerosis**. **LDL** oxidizability is believed to be strongly influenced by factors such as (a) content of preexisting lipid hydroperoxides (LOOHs) and (b) content of endogenous **antioxidants** such as alpha-tocopherol and beta-carotene. The purpose of this study was to examine the **prooxidant** role of preexisting **LDL**-LOOHs, using a recently developed method for ultrasensitive and selective LOOH analysis: high-performance liquid chromatography with mercury drop electrochemical detection (HPLC-EC). Exceedingly low detection limits for **LDL**-LOOHs have been achieved by HPLC-EC, eg., apprx 100 fmol for cholesteryl ester hydroperoxide (CEOOH). This sensitivity has allowed us to monitor **LDL**-LOOHs at levels that are undetectable by most other methods. Fresh **LDL** prepared with the utmost care to **Prevent** **autoxidation** was found to contain small, yet significant amounts of CEOOH, 6-12 pmol/mg protein. Our data suggest that these peroxides could not have arisen during **LDL** isolation or sample work-up for HPLC-EC. Incubation with GSH and phospholipid hydroperoxide glutathione **peroxidase** resulted m nearly complete reduction of the CEOOH. This **LDL** was found to be much more resistant to Cu-2+-induced **peroxidation** than material, exhibiting a lag period that was at

least six times greater. We have also determined that **LDL** becomes progressively more susceptible to Cu-2+-induced lipid **peroxidation** (as evidenced by a shortened lag) when it id preloaded with increasing amounts of photochemically generated LOOHs. Taken together, these results provide strong support for the idea that preexisting LOOHs in **LDL** are important determinants of its overall oxidizability.

L22 ANSWER 58 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:9048 BIOSIS
DOCUMENT NUMBER: PREV199598023348
TITLE: **LDL oxidation** an **antioxidant** protection of a high and low O-2 tensions.
AUTHOR(S): Hatta, Akira; Frei, Balz
CORPORATE SOURCE: Boston Univ. Sch. Med., Boston, MA USA
SOURCE: Circulation, (1994) Vol. 90, No. 4 PART 2, pp. I408. Meeting Info.: 67th Scientific Sessions of the American Heart Association Dallas, Texas, USA November 14-17, 1994 ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L22 ANSWER 59 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:528349 BIOSIS
DOCUMENT NUMBER: PREV199497541349
TITLE: **Antioxidant** vitamins and coronary artery disease risk.
AUTHOR(S): Gaziano, J. Michael
CORPORATE SOURCE: Brigham and Women's Hosp., 75 Francis St., Boston, MA 02115 USA
SOURCE: American Journal of Medicine, (1994) Vol. 97, No. 3 PART A, pp. 18S-21S. ISSN: 0002-9343.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Coronary artery disease (CAD) remains by far the leading killer of men and women in the United States, despite a 2% per year decline over the past 2 decades. While CAD becomes the leading cause of death in U.S. women after 60, it becomes so in men after age 40. Heart disease is responsible for one of every three deaths in women as well as men. Thus, any intervention that can reduce CAD risks could have a tremendous public health impact among U.S. adults. Over the past several decades, the atherogenic potential of low density lipoprotein (**LDL**) cholesterol has been clearly identified. Recent evidence suggests that **oxidation** of **LDL** may enhance its atherogenicity, raising the possibility that **antioxidant** vitamins, which inhibit the **oxidation** of **LDL**, may reduce the risk of CAD. Although **antioxidants** can preserve endothelial function, inhibit platelet aggregability, and reduce **atherosclerotic** plaque progression in animals, whether supplementation with **antioxidant** vitamins will reduce the risk of CAD in humans remains unclear. The epidemiologic studies that have explored the **antioxidant** vitamin hypothesis in humans have included descriptive and cross-sectional studies, analytic investigation using case-control and prospective cohort study designs, as well as a few small trials in secondary **prevention**. The findings from these studies are not totally consistent, but generally support the hypothesis that **antioxidant** vitamins may reduce risk of CAD. At present, therefore, **antioxidant** vitamins represent a promising, but as yet unproven, means to decrease risks of CAD. Several large-scale randomized trials will provide reliable evidence on this question over the next several years. In primary **prevention**, the recently begun Women's Health Study of 40,000 female health professionals is testing alternate-day doses of beta-carotene (50 mg) and vitamin E (600 mg), and the ongoing Physicians' Health Study of gt 22,000 male physicians is also

testing a 50 mg combination of beta-carotene, vitamin E, and vitamin C among approximately 8,000 women not eligible for the Women's Health Study due to a prior history of cardiovascular disease. These and other trials will provide reliable, direct evidence concerning the role of **antioxidant** vitamins in the primary and secondary **prevention** of cardiovascular disease in women. Such data are crucial both for individual clinical decision making as well as for formulating rational public health policies.

L22 ANSWER 60 OF 60 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1985:294529 BIOSIS
DOCUMENT NUMBER: BA79:74525
TITLE: LIPIDS LIPOPROTEINS AND ALPHA TOCOPHEROL RELATIONSHIP AND CHANGES DURING ADOLESCENCE A LONGITUDINAL STUDY.
AUTHOR(S): WIDHALM K; HOEZL M; BRUBACHER G
CORPORATE SOURCE: DEPARTMENT OF PEDIATRICS, UNIVERSITY OF VIENNA, WAEHRINGER GUERTEL 74, A-1090 VIENNA, AUSTRIA.
SOURCE: ANN NUTR METAB, (1985) 29 (1), 12-18.
CODEN: ANUMDS. ISSN: 0250-6807.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB From May 1976 to June 1982 a longitudinal study in 54 apparently healthy Austrian schoolchildren with a mean age of 11.2 yr at their 1st visit was performed. It was determined if there were any age-related changes in serum lipids, lipoproteins and .alpha.-tocopherol concentrations during adolescence and whether a permanent relationship between lipoproteins and .alpha.-tocopherol could be observed. Total cholesterol showed a significant decrease from age 11 to 14 yr in boys (from 195.5 .+-. 42.2 to 147.9 .+-. 40.3 mg/dl) as well as in girls(from 181.9 .+-. 29.7 to 144.1 .+-. 23.4 mg/dl); thereafter, a slight increase could be shown. Similar changes could be observed for **LDL** [low density lipoprotein] cholesterol. No significant sex differences were found either in total or in **LDL** cholesterol, whereas in HDL [high density lipoprotein] cholesterol concentrations, a decrease in boys between 12 and 14 yr from (58.4 .+-. 18.3 to 41.7 .+-. 10.8 mg/dl) and an increase in girls from 13 yr onwards led to significantly lower values in boys than in girls from the age of 16 yr onwards. No consistent changes could be shown for .alpha.-tocopherol blood levels. A close relationship between total cholesterol and .alpha.-tocopherol could be observed during all the investigations (0.4695 .ltoreq. P .ltoreq. 0.7300, P < 0.05) and, to a lesser degree, between **LDL** cholesterol and .alpha.-tocopherol. Significant correlations between .alpha.-tocopherol and HDL cholesterol and between .alpha.-tocopherol and triglycerides occurred only occassionally. [Early detection of abnormalities of the lipoprotein status might help to **prevent** premature onset of **atherosclerosis** .]

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(FILE 'HOME' ENTERED AT 15:51:34 ON 08 NOV 2001)

FILE 'REGISTRY' ENTERED AT 15:52:08 ON 08 NOV 2001
L1 STRUCTURE UPLOADED
L2 1 S L1
L3 12 S L2 SSS FULL

FILE 'CAPLUS' ENTERED AT 15:56:19 ON 08 NOV 2001
L4 55 S L3
L5 5 S L3/THU
L6 21 S L3 AND ?OXIDA?

FILE 'MEDLINE, BIOSIS, USPATFULL' ENTERED AT 16:03:58 ON 08 NOV 2001
L7 10 S L3 AND ?OXIDA?

```
L8           10 DUP REM L7 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 16:22:18 ON 08 NOV 2001
                E VITAMIN E
                E ALPHA TOCOPHEROL
                E TOCOPHEROL
                E .ALPHA.TOCOPHEROL
                E E
                E TOCOPHEROL
L9           238 S E3
                E .ALPHA.-TOCOPHEROL
                E ALPHA-TOCOPHEROL
                E .ALPHA.-TOCOPHEROL/CN
L10            1 S E3
                E .ALPHA.-TOCOTRIENOL/CN
L11            1 S E3
                E .ALPHA.-TOCOPHEROL/CN
L12            1 S E3

     FILE 'CAPLUS, MEDLINE, BIOSIS' ENTERED AT 16:27:31 ON 08 NOV 2001
L13        16928 S L10 OR L11 OR L12
L14         9132 S L13 AND (?OXIDA? OR ATHEROSCLERO? OR HYPERLIPOPROT?)
L15           96 S L14 AND METABOLITE
L16            0 S L14/THU
L17         7429 DUP REM L14 (1703 DUPLICATES REMOVED)
L18          551 S L14 AND (ATHEROSCLERO? OR HYPERLIPOPROT?)
L19          454 DUP REM L18 (97 DUPLICATES REMOVED)
L20          197 S L19 AND (PREVENT? OR TREAT?)
L21          115 S L20 AND LDL
L22           60 S L21 AND HUMAN
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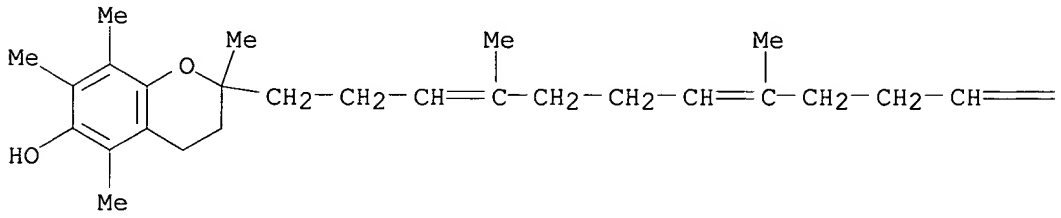
L11 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 1721-51-3 REGISTRY
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-3,7,11-tridecatrienyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 6-Chromanol, 2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-3,7,11-tridecatrienyl)- (6CI, 7CI, 8CI)
OTHER NAMES:
CN **.alpha.-Tocotrienol**
CN .xi.1-Tocopherol
CN .zeta.1-Tocopherol
CN .zeta.1-Tokoferol
CN 5,7,8-Trimethyltocotrienol
FS 3D CONCORD
DR 24960-03-0, 134931-98-9, 16833-60-6, 22625-13-4
MF C29 H44 O2
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMLIST, CIN, DDFU, DRUGU, DRUGUPDATES, EMBASE, MEDLINE, MRCK*, PROMT, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

PAGE 1-A

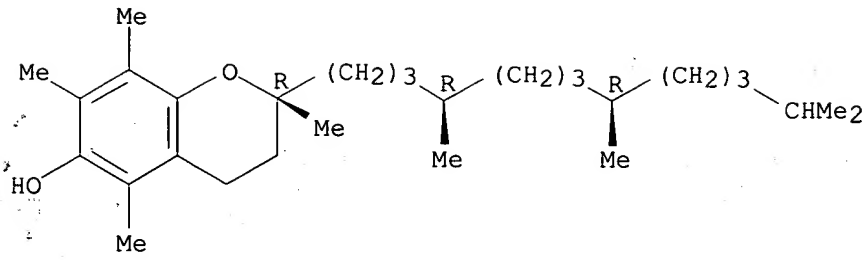


PAGE 1-B

=CMe2

L10 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 59-02-9 REGISTRY
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, [2R-[2R*(4R*,8R*)]]-
OTHER NAMES:
CN (+)-.alpha.-Tocopherol
CN (2R,4'R,8'R)-.alpha.-Tocopherol
CN (all-R)-.alpha.-Tocopherol
CN (R,R,R)-.alpha.-Tocopherol
CN **.alpha.-Tocopherol**
CN 5,7,8-Trimethyltocol
CN Almefrol
CN Covitol F 1000
CN D-.alpha.-Tocopherol
CN d-.alpha.-Tocopherol
CN Denamone
CN E 307
CN E 307 (tocopherol)
CN E-Oil 1000
CN Emipherol
CN Endo E
CN Eprolin
CN Eprolin S
CN Epsilan
CN Esorb
CN Etamican
CN Etavit
CN Evitaminum
CN Ilitia
CN Phytogermin
CN Profecundin
CN Rhenogran Ronotec 50
CN Spavit E
CN Syntopherol
CN Tenox GT 1
CN Tokopharm
CN Vascuals
CN Verrol
CN Vitamin E.alpha.
CN Vitaplex E
CN Vitayonon
CN Viteolin
FS STEREOSEARCH
DR 364-49-8, 121854-78-2, 18920-62-2
MF C29 H50 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO, TOXLIT, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.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(CH2)3
R
(CH2)3
R
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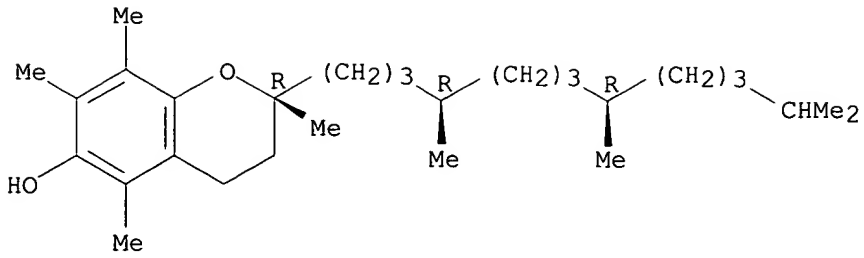
CHMe2
Me
Me
Me
HO
Me

L10 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 59-02-9 REGISTRY
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, [2R-[2R*(4R*,8R*)]]-
OTHER NAMES:
CN (+)-.alpha.-Tocopherol
CN (2R,4'R,8'R)-.alpha.-Tocopherol
CN (all-R)-.alpha.-Tocopherol
CN (R,R,R)-.alpha.-Tocopherol
CN **.alpha.-Tocopherol**
CN 5,7,8-Trimethyltocol
CN Almefrol
CN Covitol F 1000
CN D-.alpha.-Tocopherol
CN d-.alpha.-Tocopherol
CN Denamone
CN E 307
CN E 307 (tocopherol)
CN E-Oil 1000
CN Emipherol
CN Endo E
CN Eprolin
CN Eprolin S
CN Epsilan
CN Esorb
CN Etamican
CN Etavit
CN Evitaminum
CN Ilitia
CN Phytogermin
CN Profecundin
CN Rhenogran Ronotec 50
CN Spavit E
CN Syntopherol
CN Tenox GT 1
CN Tokopharm
CN Vascuals
CN Verrol
CN Vitamin E.alpha.
CN Vitaplex E
CN Vitayonon
CN Viteolin
FS STEREOSEARCH
DR 364-49-8, 121854-78-2, 18920-62-2
MF C29 H50 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO, TOXLIT, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.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Me
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R
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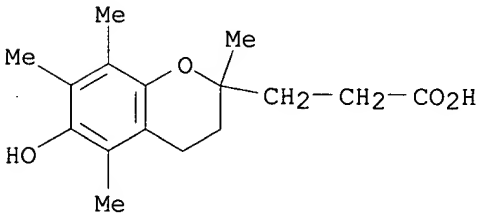
L8 ANSWER 1 OF 10 USPATFULL
ACCESSION NUMBER: 2001:182622 USPATFULL
TITLE: Use of gamma-tocopherol and its **oxidative** metabolite LLU-alpha in the treatment of disease
INVENTOR(S): Wechter, William J., Ojai, CA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001031782	A1	20011018
APPLICATION INFO.:	US 2001-814330	A1	20010321 (9)

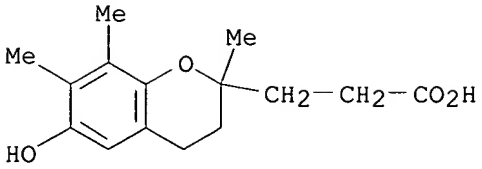
RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-461645, filed on 14 Dec 1999, GRANTED, Pat. No. US 6242479 Continuation of Ser. No. US 1998-215608, filed on 17 Dec 1998, GRANTED, Pat. No. US 6048891
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KNOBBE MARTENS OLSON & BEAR LLP, 620 NEWPORT CENTER DRIVE, SIXTEENTH FLOOR, NEWPORT BEACH, CA, 92660
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 1667
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is generally related to the discovery of the therapeutic benefit of administering .gamma.-tocopherol and .gamma.-tocopherol derivatives. More specifically, the use of .gamma.-tocopherol and racemic LLU-.alpha., (S)-LLU-.alpha., or .gamma.-tocopherol derivatives as **antioxidants** and nitrogen oxide scavengers which treat and prevent high blood pressure, thromboembolic disease, cardiovascular disease, cancer, natriuretic disease, the formation of neuropathological lesions, and a reduced immune system response are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **4072-32-6P**
(prepn. and reaction; .gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 4072-32-6 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)

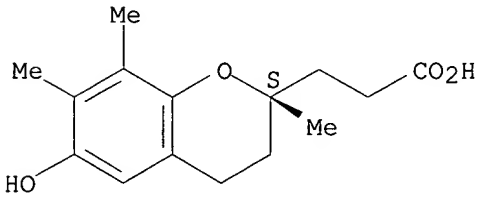


IT **178167-75-4P**
(.gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-75-4 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl- (9CI) (CA INDEX NAME)



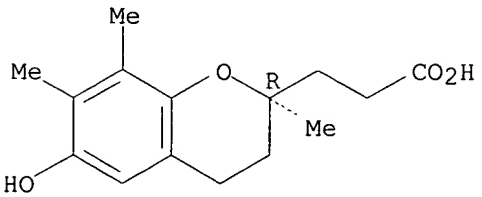
IT **178167-88-9P**
(.gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-88-9 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **178167-89-0P**
(.gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-89-0 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



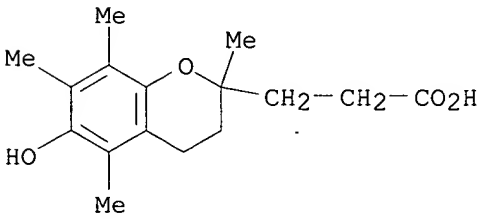
L8 ANSWER 2 OF 10 USPATFULL

ACCESSION NUMBER:	2001:82804 USPATFULL
TITLE:	Use of .gamma.-tocopherol and its **oxidative** metabolite LLU-.alpha. in the treatment of disease
INVENTOR(S):	Wechter, William J., Redlands, CA, United States
PATENT ASSIGNEE(S):	Loma Linda University Medical Center, Loma Linda, CA, United States (U.S. corporation)

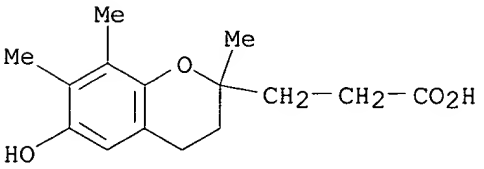
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6242479	B1	20010605
APPLICATION INFO.:	US 1999-461645		19991214 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1998-215608, filed on 17 Dec 1998, now patented, Pat. No. US 6048891		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Henley, III, Raymond		
LEGAL REPRESENTATIVE:	Knobbe, Martens, Olson & Bear, LLP		
NUMBER OF CLAIMS:	54		

EXEMPLARY CLAIM: 1
LINE COUNT: 1803
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is generally related to the discovery of the therapeutic benefit of administering .gamma.-tocopherol and .gamma.-tocopherol derivatives. More specifically, the use of .gamma.-tocopherol and racemic LLU-.alpha., (S)-LLU-.alpha., or .gamma.-tocopherol derivatives as **antioxidants** and nitrogen oxide scavengers which treat and prevent high blood pressure, thromboembolic disease, cardiovascular disease, cancer, natriuretic disease, the formation of neuropathological lesions, and a reduced immune system response are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **4072-32-6P**
(prepn. and reaction; .gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 4072-32-6 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)

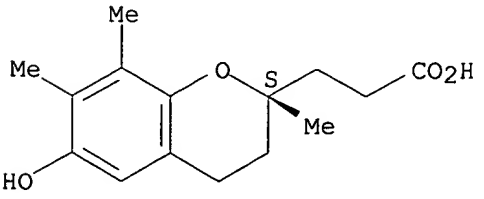


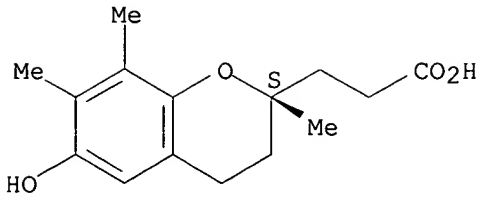
IT **178167-75-4P**
(.gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-75-4 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl- (9CI) (CA INDEX NAME)



IT **178167-88-9P**
(.gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-88-9 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2S)- (9CI) (CA INDEX NAME)

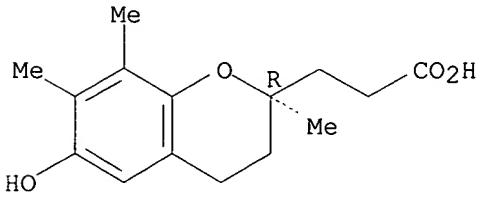
Absolute stereochemistry.





IT **178167-89-0P**
(.gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-89-0 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 3 OF 10 USPATFULL

ACCESSION NUMBER:	2000:157451 USPATFULL
TITLE:	Natriuretic compounds
INVENTOR(S):	Wechter, William J., Redlands, CA, United States Murray, David E., Redlands, CA, United States Kantoci, Darko, Redlands, CA, United States Levine, Barry H., Oakland, CA, United States Benaksas, Elaine J., Yorba Linda, CA, United States
PATENT ASSIGNEE(S):	Loma Linda University Medical Center, Loma Linda, CA, United States (U.S. corporation)

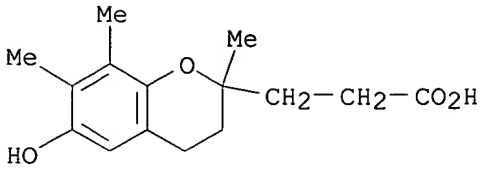
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6150402		20001121	
APPLICATION INFO.:	US 1994-290430		19940815	(8)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Owens, Amelia			
LEGAL REPRESENTATIVE:	Knobbe, Martens, Olson & Bear, LLP.			
NUMBER OF CLAIMS:	11			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 5 Drawing Page(s)			
LINE COUNT:	1509			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds, methods and compositions are provided for inducing natriuresis in a mammal. Methods for isolating and synthesizing the natriuretic compounds are also provided. Therapeutic methods using the natriuretic compounds are also provided. The natriuretic compounds are capable of inducing sodium excretion in a mammal without inducing corresponding prolongated potassium excretion.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **178167-75-4P**
(natriuretic cyclic compds. for stimulating sodium excretion in treatment of hypertension, heart diseases, and HIV infection)
RN 178167-75-4 USPATFULL

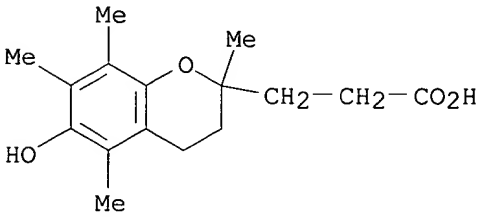
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl- (9CI) (CA INDEX NAME)



IT **4072-32-6P 178167-88-9P 178167-89-0P**
(natriuretic cyclic compds. for stimulating sodium excretion in treatment of hypertension, heart diseases, and HIV infection)

RN 4072-32-6 USPATFULL

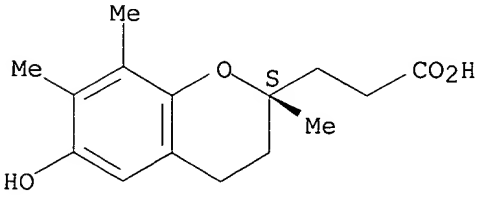
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



RN 178167-88-9 USPATFULL

CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2S)- (9CI) (CA INDEX NAME)

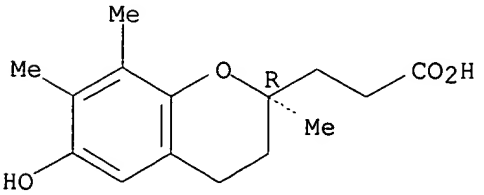
Absolute stereochemistry.



RN 178167-89-0 USPATFULL

CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 4 OF 10 USPATFULL

ACCESSION NUMBER: 2000:84320 USPATFULL

TITLE: Natriuretic compounds

INVENTOR(S):	Wechter, William J., Redlands, CA, United States Murray, David E., Redlands, CA, United States Kantoci, Darko, Redlands, CA, United States Levine, Barry H., Oakland, CA, United States Benaksas, Elaine J., Yorba Linda, CA, United States
PATENT ASSIGNEE(S):	Loma Linda University Medical, Loma Linda, CA, United States (U.S. corporation)

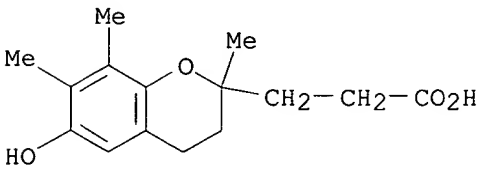
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6083982		20000704
APPLICATION INFO.:	US 1998-57731		19980409 (9)
RELATED APPLN. INFO.:	Division of Ser. No. US 1994-290430, filed on 15 Aug 1994		

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Owens, Amelia
LEGAL REPRESENTATIVE: Knobble, Martens, Olson & Bear, LLP.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1557
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

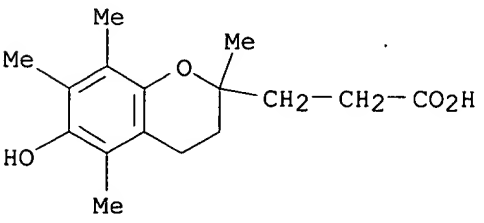
AB Compounds, methods and compositions are provided for inducing natriuresis in a mammal. Methods for isolating and synthesizing the natriuretic compounds are also provided. Therapeutic methods using the natriuretic compounds are also provided. The natriuretic compounds are capable of inducing sodium excretion in a mammal without inducing corresponding prolonged potassium excretion.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **178167-75-4P**
(natriuretic cyclic compds. for stimulating sodium excretion in treatment of hypertension, heart diseases, and HIV infection)
RN 178167-75-4 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl- (9CI) (CA INDEX NAME)

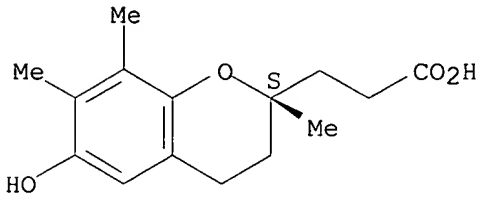


IT **4072-32-6P 178167-88-9P 178167-89-0P**
(natriuretic cyclic compds. for stimulating sodium excretion in treatment of hypertension, heart diseases, and HIV infection)
RN 4072-32-6 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



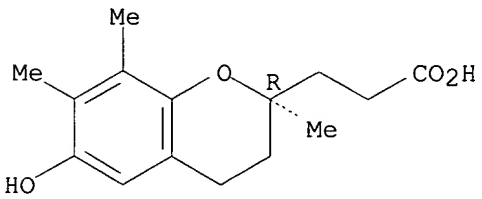
RN 178167-88-9 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 178167-89-0 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 5 OF 10 USPATFULL

ACCESSION NUMBER:	2000:44130 USPATFULL
TITLE:	Use of .gamma.-tocopherol and its **oxidative** metabolite LLU-.alpha. in the treatment of natriuretic disease
INVENTOR(S):	Wechter, William J., Redlands, CA, United States
PATENT ASSIGNEE(S):	Loma Linda University Medical Center, Loma Linda, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6048891		20000411
APPLICATION INFO.:	US 1998-215608		19981217 (9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Henley, III, Raymond
LEGAL REPRESENTATIVE:	Knobbe, Martens, Olson & Bear, LLP.
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1
LINE COUNT:	1686

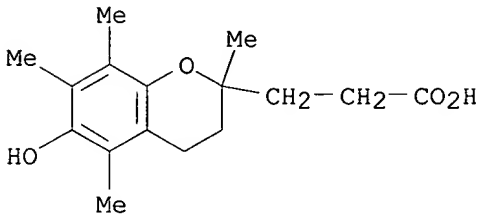
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is generally related to the discovery of the therapeutic benefit of administering .gamma.-tocopherol and .gamma.-tocopherol derivatives. More specifically, the use of .gamma.-tocopherol and racemic LLU-.alpha., (S)-LLU-.alpha., or .gamma.-tocopherol derivatives as **antioxidants** and nitrogen oxide scavengers which treat and prevent high blood pressure, thromboembolic disease, cardiovascular disease, cancer, natriuretic disease, the formation of neuropathological lesions, and a reduced immune system response are disclosed.

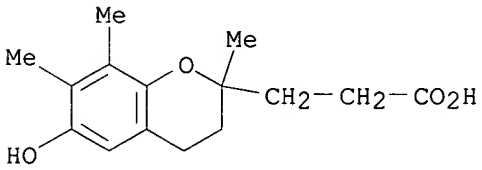
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **4072-32-6P**

(prepn. and reaction; .gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 4072-32-6 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)

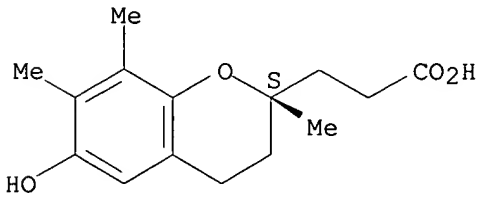


IT **178167-75-4P**
(.gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-75-4 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl- (9CI) (CA INDEX NAME)



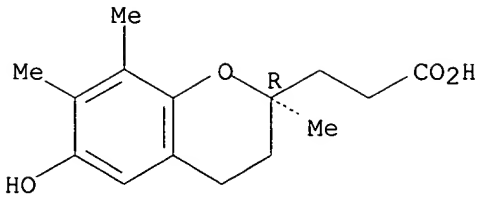
IT **178167-88-9P**
(.gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-88-9 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **178167-89-0P**
(.gamma.-tocopherol and oxidative metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-89-0 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 6 OF 10 MEDLINE
ACCESSION NUMBER: 2001082879 MEDLINE
DOCUMENT NUMBER: 20469528 PubMed ID: 11013295
TITLE: Urinary alpha-tocopherol metabolites in alpha-tocopherol transfer protein-deficient patients.
AUTHOR: Schuelke M; Elsner A; Finckh B; Kohlschutter A; Hubner C; Brigelius-Flohe R
CORPORATE SOURCE: Department of Neuropediatrics, Charite University Hospital, Humboldt University Berlin, D-13353 Berlin, Germany.
SOURCE: JOURNAL OF LIPID RESEARCH, (2000 Oct) 41 (10) 1543-51.
Journal code: IX3. ISSN: 0022-2275.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010105

AB Patients with alpha-tocopherol transfer protein (alpha-TTP) defects experience neurological symptoms characteristic of vitamin E deficiency and depend on continuous high alpha-tocopherol supplements. We investigated the excretion of 2,5,7, 8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman (alpha-CEHC), a urinary metabolite of alpha-tocopherol, as a putative marker for the alpha-tocopherol status of alpha-TTP-deficient patients and control subjects. In three patients vitamin E supplementation was stopped for short periods of time, during which plasma alpha-tocopherol concentrations and urinary alpha-CEHC excretion were measured. In the patients, plasma alpha-tocopherol decreased below normal (<5 micromol/l) but alpha-CEHC excretion remained above the range of unsupplemented control subjects (0.118-0.306 mg/day, n = 6). In healthy subjects, however, alpha-CEHC excretion was increased only after surpassing a plasma alpha-tocopherol threshold of 30-40 micromol/l. Such a threshold did not exist in patients. The general mechanism of alpha-tocopherol degradation did not appear to differ between patients and control subjects. The presumed mechanism of omega- and subsequent beta-**oxidation** was supported by the detection of alpha- CPHC, an alpha -CEHC homolog with a side chain longer by 3 carbon atoms, both in supplemented patients and in control subjects.

L8 ANSWER 7 OF 10 MEDLINE
ACCESSION NUMBER: 2000464641 MEDLINE
DOCUMENT NUMBER: 20470493 PubMed ID: 11019814
TITLE: A new method for the analysis of urinary vitamin E metabolites and the tentative identification of a novel group of compounds.
AUTHOR: Pope S A; Clayton P T; Muller D P
CORPORATE SOURCE: Biochemistry, Endocrinology and Metabolism Unit, Institute of Child Health, University College London, United Kingdom.
SOURCE: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (2000 Sep 1) 381 (1) 8-15.
Journal code: 6SK; 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001017

AB There is currently interest in measuring urinary metabolites of vitamin E. It has been suggested that alpha-to-copheronolactone (alphaTL), with an oxidized chroman ring, may be an indicator of in vivo **oxidative** stress and 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman (alpha-CEHC), with a shortened side chain but intact hydroxychroman ring, may provide a measure of adequate or excess vitamin E status. To date, methods in the literature have tended to concentrate on the estimation of single metabolites. We describe the establishment and validation of a relatively simple and reproducible method to extract and quantitate a range of vitamin E metabolites using 0.5 ml of human urine. The vitamin E metabolites were extracted from urine using solid phase extraction cartridges, deconjugated enzymatically, and analyzed using gas chromatography-mass spectrometry. Using this method we have identified alphaTL and the CEHC metabolites derived from alpha-, delta-, and gamma-tocopherol. In addition we have tentatively identified a novel group of vitamin E metabolites, which are related to the CEHCs but have three extra carbons in the side chain. The possibility of the artifactual **oxidation** of alpha-CEHC to alphaTL during the assay procedure is also discussed.

L8 ANSWER 8 OF 10 MEDLINE
ACCESSION NUMBER: 96094712 MEDLINE
DOCUMENT NUMBER: 96094712 PubMed ID: 7495255
TITLE: Novel urinary metabolite of alpha-tocopherol, 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman, as an indicator of an adequate vitamin E supply?.
AUTHOR: Schultz M; Leist M; Petrzika M; Gassmann B; Brigelius-Flohe R
CORPORATE SOURCE: Department of Vitamins and Atherosclerosis, German Institute of Human Nutrition, Potsdam-Rehbrucke, Germany.
SOURCE: AMERICAN JOURNAL OF CLINICAL NUTRITION, (1995 Dec) 62 (6 Suppl) 1527S-1534S.
Journal code: 3EY; 0376027. ISSN: 0002-9165.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960217
Last Updated on STN: 19960217
Entered Medline: 19960111

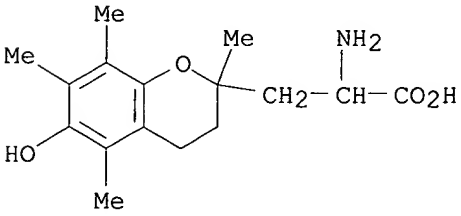
AB Previously, the metabolism of alpha-tocopherol was considered to involve the opening of the chroman structure because of its **oxidation** to tocopherylquinone. In contrast, we describe here 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman (alpha-CEHC) as the major urinary metabolite of alpha-tocopherol that appears in human urine after vitamin E supplementation. It is formed directly from alpha-tocopherol without previous **oxidative** splitting of the chroman ring. The correlation of alpha-tocopherol intake, plasma alpha-tocopherol concentrations, and urinary excretion of alpha-CEHC in human volunteers supplemented with RRR-alpha-tocopherol dosages ranging from 0 to 800 mg/d was examined. HPLC and gas chromatography-mass spectroscopy analysis revealed that alpha-CEHC was only excreted when a plasma threshold of 7-9 mumol alpha-tocopherol/g total lipid was exceeded. This concentration was obtained by a daily intake of approximately 50-150 mg alpha-tocopherol. We suggest that alpha-CEHC excretion indicates a saturated binding capacity of vitamin E in the plasma and thus may be considered to be a marker of optimum vitamin E intake.

L8 ANSWER 9 OF 10 USPATFULL
ACCESSION NUMBER: 87:65394 USPATFULL
TITLE: Chroman compounds useful as analgerics and **antioxidants**
INVENTOR(S): Shiono, Manzo, Kurashiki, Japan
Fujita, Yoshiji, Kurashiki, Japan
Nishida, Takashi, Kurashiki, Japan
PATENT ASSIGNEE(S): Kuraray Co., Ltd., Kurashiki, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4694090		19870915
APPLICATION INFO.:	US 1984-679455		19841207 (6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Chan, Nicky
LEGAL REPRESENTATIVE: Burns, Doane, Swecker & Mathis
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 938
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel chroman compounds which have excellent **antioxidant** activity and/or analgesic activity or serve as precursors for such active compounds are provided. There are also provided uses of these active compounds as an **antioxidant** and/or analgesic.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **103945-99-9**
(antioxidant activity of)
RN 103945-99-9 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, .alpha.-amino-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-, monosodium salt (9CI) (CA INDEX NAME)



IT **96909-73-8P 97322-21-9P 97322-27-5P**
(prepn. of, as analgesic and antioxidant)
RN 96909-73-8 USPATFULL
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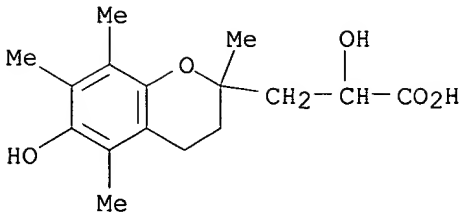

RN 97322-21-9 USPATFULL
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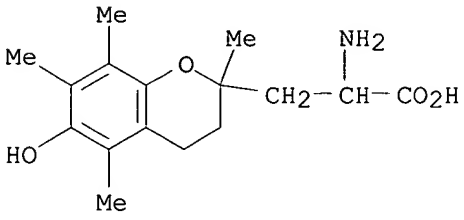

RN 97322-27-5 USPATFULL
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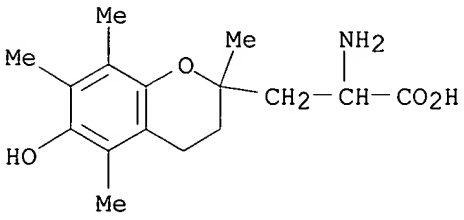


● HCl

L8 ANSWER 10 OF 10 USPATFULL

ACCESSION NUMBER:	80:4512 USPATFULL
TITLE:	Combating arthropods with 2-substituted-chroman-4-ones
INVENTOR(S):	Kabbe, Hans-Joachim, Leverkusen, Germany, Federal Republic of Roessler, Peter, Berg.Gladbach, Germany, Federal Republic of
PATENT ASSIGNEE(S):	Bayer Aktiengesellschaft, Leverkusen, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4185112		19800122	
APPLICATION INFO.:	US 1978-947285		19780929	(5)

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1977-2745306	19771007

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted
PRIMARY EXAMINER: Turner, V. D.
LEGAL REPRESENTATIVE: Sprung, Felfe, Horn, Lynch & Kramer
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
LINE COUNT: 663
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Known 2-substituted-chroman-4-ones of the formula ##STR1## wherein R.sup.1 to R.sup.4 each independently is hydrogen, various hydrocarbyl groups, alkoxycarbonyl, carboxyl or aminoalkyl, or

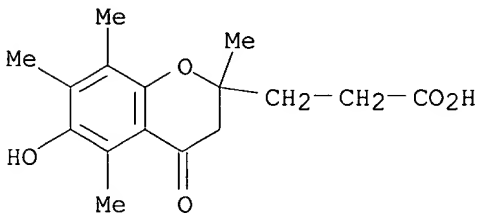
R.sup.2 can also be an amino radical, or

R.sup.1 and R.sup.2 can complete a carbocyclic or heterocyclic ring, and

R.sup.5 to R.sup.8 each independently is hydrogen, halogen hydroxyl, nitro, cyano, carboxyl, various hydrocarbyl or hydrocarbyloxy groups, alkoxycarbonyl, alkylamino or acylamino

are effective in combating arthropods, being applied to the arthropods or their habitat such as soil, plants and domesticated animals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **69367-17-5P**
(prepn. and acaricidal and insecticidal activity of)
RN 69367-17-5 USPATFULL
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-4-oxo- (9CI) (CA INDEX NAME)



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L3 12 S L2 SSS FULL

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L5 5 S L3/THU
L6 21 S L3 AND ?OXIDA?

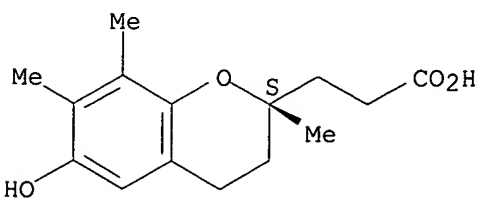
FILE 'MEDLINE, BIOSIS, USPATFULL' ENTERED AT 16:03:58 ON 08 NOV 2001
L7 10 S L3 AND ?OXIDA?
L8 10 DUP REM L7 (0 DUPLICATES REMOVED)

L6 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:759916 CAPLUS
DOCUMENT NUMBER: 134:36796
TITLE: .gamma.-Tocopherol and its major metabolite, in contrast to .alpha.-tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells
AUTHOR(S): Jiang, Qing; Elson-Schwab, Ilan; Courtemanche, Chantal; Ames, Bruce N.
CORPORATE SOURCE: Division of Biochemistry and Molecular Biology, University of California, Berkeley, CA, 94720, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (2000), 97(21), 11494-11499
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclooxygenease-2 (COX-2)-catalyzed synthesis of prostaglandin E2 (PGE2) plays a key role in inflammation and its assocd. diseases, such as cancer and vascular heart disease. Here we report that .gamma.-tocopherol (.gamma.T) reduced PGE2 synthesis in both lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages and IL-1.beta.-treated A549 human epithelial cells with an apparent IC50 of 7.5 and 4 .mu.M, resp. The major metabolite of dietary .gamma.T, 2,7,8-trimethyl-2-(.beta.-carboxyethyl)-6-hydroxychroman (.gamma.-CEHC), also exhibited an inhibitory effect, with an IC50 of .apprxeq.30 .mu.M in these cells. In contrast, .alpha.-tocopherol at 50 .mu.M slightly reduced (25%) PGE2 formation in macrophages, but had no effect in epithelial cells. The inhibitory effects of .gamma.T and .gamma.-CEHC stemmed from their inhibition of COX-2 activity, rather than affecting protein expression or substrate availability, and appeared to be independent of **antioxidant** activity. .gamma.-CEHC also inhibited PGE2 synthesis when exposed for 1 h to COX-2-preinduced cells followed by the addn. of arachidonic acid (AA), whereas under similar conditions, .gamma.T required an 8- to 24-h incubation period to cause the inhibition. The inhibitory potency of .gamma.T and .gamma.-CEHC was diminished by an increase in AA concn., suggesting that they might compete with AA at the active site of COX-2. We also obsd. a moderate redn. of nitrite accumulation and suppression of inducible nitric oxide synthase expression by .gamma.T in lipopolysaccharide-treated macrophages. These findings indicate that .gamma.T and its major metabolite possess anti-inflammatory activity and that .gamma.T at physiol. concns. may be important in human disease prevention.

IT **178167-88-9**
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(.gamma.-Tocopherol and its major metabolite inhibit cyclooxygenase activity in macrophages and epithelial cells)
RN 178167-88-9 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



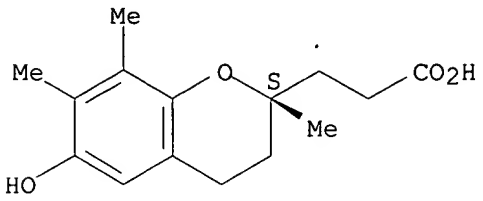
REFERENCE COUNT: 55
REFERENCE(S): (1) Ames, B; Proc Natl Acad Sci USA 1993, V90, P7915 CAPLUS
(2) Behrens, W; J Am Coll Nutr 1986, V5, P91 CAPLUS
(3) Bieri, J; Am J Clin Nutr 1974, V27, P980 CAPLUS
(4) Bieri, J; J Nutr 1974, V104, P850 CAPLUS
(5) Brigelius-Flohe, R; FASEB J 1999, V13, P1145 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d 16 ibib abs hitstr 1-
YOU HAVE REQUESTED DATA FROM 21 ANSWERS - CONTINUE? Y/(N):y

L6 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:759916 CAPLUS
DOCUMENT NUMBER: 134:36796
TITLE: .gamma.-Tocopherol and its major metabolite, in contrast to .alpha.-tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells
AUTHOR(S): Jiang, Qing; Elson-Schwab, Ilan; Courtemanche, Chantal; Ames, Bruce N.
CORPORATE SOURCE: Division of Biochemistry and Molecular Biology, University of California, Berkeley, CA, 94720, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (2000), 97(21), 11494-11499
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclooxygenease-2 (COX-2)-catalyzed synthesis of prostaglandin E2 (PGE2) plays a key role in inflammation and its assocd. diseases, such as cancer and vascular heart disease. Here we report that .gamma.-tocopherol (.gamma.T) reduced PGE2 synthesis in both lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages and IL-1.beta.-treated A549 human epithelial cells with an apparent IC50 of 7.5 and 4 .mu.M, resp. The major metabolite of dietary .gamma.T, 2,7,8-trimethyl-2-(.beta.-carboxyethyl)-6-hydroxychroman (.gamma.-CEHC), also exhibited an inhibitory effect, with an IC50 of .apprxeq.30 .mu.M in these cells. In contrast, .alpha.-tocopherol at 50 .mu.M slightly reduced (25%) PGE2 formation in macrophages, but had no effect in epithelial cells. The inhibitory effects of .gamma.T and .gamma.-CEHC stemmed from their inhibition of COX-2 activity, rather than affecting protein expression or substrate availability, and appeared to be independent of **antioxidant** activity. .gamma.-CEHC also inhibited PGE2 synthesis when exposed for 1 h to COX-2-preinduced cells followed by the addn. of arachidonic acid (AA), whereas under similar conditions, .gamma.T required an 8- to 24-h incubation period to cause the inhibition. The inhibitory potency of .gamma.T and .gamma.-CEHC was diminished by an increase in AA concn., suggesting that they might compete with AA at the active site of COX-2. We also obsd. a moderate redn. of nitrite accumulation and suppression of inducible nitric oxide synthase expression by .gamma.T in lipopolysaccharide-treated macrophages. These findings indicate that .gamma.T and its major metabolite possess anti-inflammatory activity and that .gamma.T at physiol. concns. may be important in human disease prevention.
IT **178167-88-9**
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(.gamma.-Tocopherol and its major metabolite inhibit cyclooxygenase activity in macrophages and epithelial cells)
RN 178167-88-9 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-,

(2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



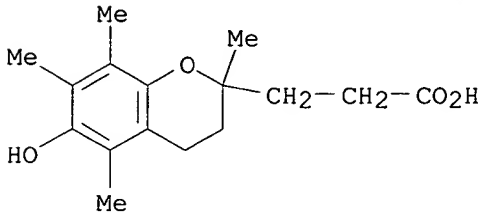
REFERENCE COUNT: 55
REFERENCE(S):
(1) Ames, B; Proc Natl Acad Sci USA 1993, V90, P7915 CAPLUS
(2) Behrens, W; J Am Coll Nutr 1986, V5, P91 CAPLUS
(3) Bieri, J; Am J Clin Nutr 1974, V27, P980 CAPLUS
(4) Bieri, J; J Nutr 1974, V104, P850 CAPLUS
(5) Brigelius-Flohe, R; FASEB J 1999, V13, P1145 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:728570 CAPLUS
DOCUMENT NUMBER: 134:16205
TITLE: Urinary .alpha.-tocopherol metabolites in .alpha.-tocopherol transfer protein-deficient patients
AUTHOR(S): Schuelke, Markus; Elsner, Angelika; Finckh, Barbara; Kohlschutter, Alfried; Hubner, Christoph; Brigelius-Flohe, Regina
CORPORATE SOURCE: Department of Neuropediatrics, Charite University Hospital, Humboldt University Berlin, Berlin, D-13353, Germany
SOURCE: J. Lipid Res. (2000), 41(10), 1543-1551
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Patients with .alpha.-tocopherol transfer protein (.alpha.-TTP) defects experience neurol. symptoms characteristic of vitamin E deficiency and depend on continuous high .alpha.-tocopherol supplements. The authors investigated the excretion of 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman (.alpha.-CEHC), a urinary metabolite of .alpha.-tocopherol, as a putative marker for the .alpha.-tocopherol status of .alpha.-TTP-deficient patients and control subjects. In three patients vitamin E supplementation was stopped for short periods of time, during which plasma .alpha.-tocopherol concns. and urinary .alpha.-CEHC excretion were measured. In the patients, plasma .alpha.-tocopherol decreased below normal (<5 .mu.mol/l) but .alpha.-CEHC excretion remained above the range of unsupplemented control subjects (0.118-0.306 mg/day). In healthy subjects, however, .alpha.-CEHC excretion was increased only after surpassing a plasma .alpha.-tocopherol threshold of 30-40 .mu.mol/l. Such a threshold did not exist in patients. The general mechanism of .alpha.-tocopherol degrdn. did not appear to differ between patients and control subjects. The presumed mechanism of .omega.- and subsequent .beta.-oxidn. was supported by the detection of .alpha.-CPHC, an .alpha.-CEHC homolog with a side chain longer by 3 carbon atoms, both in supplemented patients and in control subjects.

IT **4072-32-6**
RL: ANT (Analyte); BOC (Biological occurrence); BUU (Biological use, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(urinary .alpha.-tocopherol metabolite in .alpha.-tocopherol transfer

protein-deficient (ataxia with isolated vitamin E deficiency) humans)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



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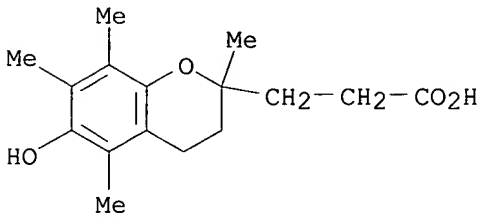
(8) Copp, R; Brain Res 1999, V822, P80 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:709158 CAPLUS
DOCUMENT NUMBER: 134:85445
TITLE: Long-term effects of vitamin E, vitamin C, and combined supplementation on urinary 7-hydro-8-oxo-2'-deoxyguanosine, serum cholesterol **oxidation** products, and **oxidation** resistance of lipids in nondepleted men
AUTHOR(S): Porkkala-Sarataho, Elina; Salonen, Jukka T.; Nyyssonen, Kristiina; Kaikkonen, Jari; Salonen, Riitta; Ristonmaa, Ulla; Diczfalusy, Ulf; Brigelius-Flohe, Regina; Loft, Steffen; Poulsen, Henrik E.
CORPORATE SOURCE: Research Institute of Public Health, University of Kuopio, Kuopio, 70211, Finland
SOURCE: Arterioscler., Thromb., Vasc. Biol. (2000), 20(9), 2087-2093
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of vitamin C (500 mg of slow release ascorbate/day), vitamin E (182 mg of RRR-.alpha.-tocopherol acetate/day), and the combination of both (E+C) were evaluated. Lipid peroxidn. measurements were carried out in 48 men at entry and at 12 and 36 mo. Compared with placebo, vitamin E and the E+C combination increased blood plasma lipid-standardized .alpha.-tocopherol levels during the first 12 mo by 68.2 and 65.2%, resp., and decreased blood serum 7.beta.-hydroxycholesterol by 50.4 and 44.0%, resp. The net change in lipid-standardized .alpha.-tocopherol levels was 63.8% after 36 mo of vitamin E supplementation and 43.3% for the E+C combination. Vitamin C elevated plasma total ascorbate levels by 30.1% at 12 mo and by 91.1% at 36 mo. Neither vitamin E, vitamin C, nor the E+C combination influenced the urinary excretion of 8-oxo-2'-deoxyguanosine or the **antioxidative** capacity of blood plasma. Vitamin E and the E+C combination enhanced the oxidn. resistance of isolated lipoproteins and total blood serum lipids. Thus, long-term dietary supplementation of nondepleted men with reasonable doses of vitamin E alone or in combination with slow-release vitamin C decreases lipid peroxidn. in vitro and in vivo, whereas relatively high doses of vitamin C alone do not.

IT **4072-32-6**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(dietary vitamins E, C and E+C supplements effects on urinary 7-hydro-8-oxo-2'-deoxyguanosine, blood serum cholesterol oxidn. products and lipid oxidn. resistance in nondepleted men)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



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REFERENCE(S):
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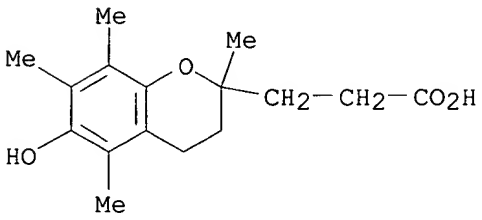
(3) Brown, A; Atherosclerosis 1999, V142, P1 CAPLUS
(4) Carpenter, K; Biochim Biophys Acta 1995, V1256, P141 CAPLUS
(5) Clare, K; Atherosclerosis 1995, V118, P67 CAPLUS
(6) Colles, S; J Lipid Res 1996, V37, P2018 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:605350 CAPLUS
DOCUMENT NUMBER: 134:2274
TITLE: A New Method for the Analysis of Urinary Vitamin E Metabolites and the Tentative Identification of a Novel Group of Compounds
AUTHOR(S): Pope, S. A. S.; Clayton, P. T.; Muller, D. P. R.
CORPORATE SOURCE: Biochemistry, Endocrinology and Metabolism Unit, Institute of Child Health, University College London, London, UK
SOURCE: Arch. Biochem. Biophys. (2000), 381(1), 8-15
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB There is currently interest in measuring urinary metabolites of vitamin E. It has been suggested that .alpha.-tocopheronolactone (.alpha.TL), with an oxidized chroman ring, may be an indicator of in vivo **oxidative** stress and 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman (.alpha.-CEHC), with a shortened side chain but intact hydroxychroman ring, may provide a measure of adequate or excess vitamin E status. To date, methods in the literature have tended to conc. on the estn. of single metabolites. We describe the establishment and validation of a relatively simple and reproducible method to ext. and quantitate a range of vitamin E metabolites using 0.5 mL of human urine. The vitamin E metabolites were extd. from urine using solid phase extn. cartridges, deconjugated enzymically, and analyzed using gas chromatog.-mass spectrometry. Using this method we have identified .alpha.TL and the CEHC metabolites derived from .alpha.-, .delta.-, and .gamma.-tocopherol. In addn. we have tentatively identified a novel group of vitamin E metabolites, which are related to the CEHCs but have three extra carbons in the side chain. The possibility of the artifactual oxidn. of .alpha.-CEHC to .alpha.TL during the assay procedure is also discussed. (c) 2000 Academic Press.
IT **4072-32-6**

RL: ANT (Analyte); MFM (Metabolic formation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(a new method for anal. of urinary vitamin E metabolites and tentative identification of a novel group of compds.)

RN 4072-32-6 CAPLUS

CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



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(3) Burton, G; Arch Biochem Biophys 1983, V221, P281 CAPLUS
(5) Chiku, S; J Lipid Res 1984, V25, P40 CAPLUS
(6) Fabiny, D; Clin Chem 1971, V17, P696 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:420456 CAPLUS

DOCUMENT NUMBER: 133:99955

TITLE: Occurrence and determination of a natriuretic hormone, 2,7,8-trimethyl-2-(.beta.-carboxyethyl)-6-hydroxy chroman, in rat plasma, urine, and bile

AUTHOR(S): Hattori, Akihiro; Fukushima, Takeshi; Imai, Kazuhiro

CORPORATE SOURCE: Department of Bio-Analytical Chemistry, Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, 113-0033, Japan

SOURCE: Anal. Biochem. (2000), 281(2), 209-215
CODEN: ANBCA2; ISSN: 0003-2697

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

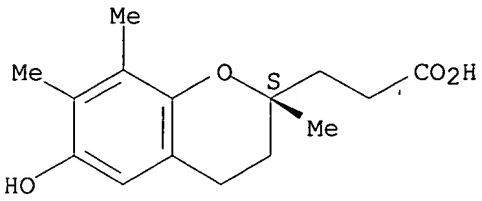
LANGUAGE: English

AB The occurrence of a new natriuretic hormone, 2,7,8-trimethyl-2-(.beta.-carboxyethyl)-6-hydroxy chroman (LLU-.alpha., .gamma.-CEHC) in rat plasma was demonstrated and its concn. was detd. using a coupled-column HPLC with a fluorometric derivatization with 4-N,N-dimethylaminosulfonyl-7-piperazino-2,1,3-benzoxadiazole (DBD-PZ) followed by O-acetylation. The concn. of LLU-.alpha. was 328.+-.113 nM in rat plasma (N = 5). LLU-.alpha. was found in not only urine, but also bile, suggesting an enterohepatic circulation in body. We also assigned the configuration at C-2 of LLU-.alpha. in these biol. fluids as (S)-form by an HPLC with a chiral column. The LLU-.alpha. concn. decreased significantly by fasting for 3 days ($P < 0.01$). These results support the possibility that LLU-.alpha. is produced from .gamma.-tocopherol in diet via **oxidative** metab. without racemization. (c) 2000 Academic Press.

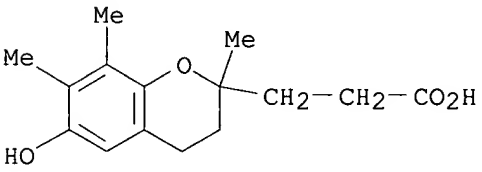
IT **178167-88-9**, (S)-LLU-.alpha.
RL: ANT (Analyte); BOC (Biological occurrence); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(occurrence and detn. of a natriuretic hormone, 2,7,8-trimethyl-2-(.beta.-carboxyethyl)-6-hydroxy chroman, in rat plasma, urine, and bile)

RN 178167-88-9 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **178167-75-4**
RL: RCT (Reactant)
(occurrence and detn. of a natriuretic hormone, 2,7,8-trimethyl-2-(.beta.-carboxyethyl)-6-hydroxy chroman, in rat plasma, urine, and bile)
RN 178167-75-4 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl- (9CI) (CA INDEX NAME)



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REFERENCE(S):
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(5) Kantoci, D; J Pharmacol Exp Ther 1997, V282, P648 CAPLUS
(6) Kayden, H; J Lipid Res 1993, V34, P343 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:238052 CAPLUS
DOCUMENT NUMBER: 132:260686
TITLE: Use of .gamma.-tocopherol and its **oxidative** metabolite LLU-.alpha. in the treatment of natriuretic disease
INVENTOR(S): Wechter, William J.
PATENT ASSIGNEE(S): Loma Linda University Medical Center, USA
SOURCE: U.S., 21 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

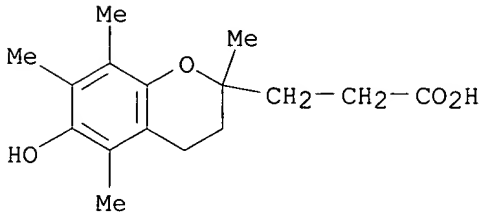
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6048891	A	20000411	US 1998-215608	19981217
US 6242479	B1	20010605	US 1999-461645	19991214
WO 2000035444	A1	20000622	WO 1999-US30100	19991216

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,

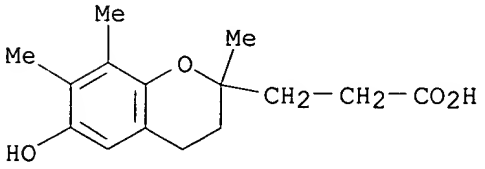
PT, SE
EP 1140065 A1 20011010 EP 1999-968905 19991216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
US 2001031782 A1 20011018 US 2001-814330 20010321
PRIORITY APPLN. INFO.: US 1998-215608 A1 19981217
US 1999-461645 A1 19991214
WO 1999-US30100 W 19991216
OTHER SOURCE(S): MARPAT 132:260686

AB The invention is generally related to the discovery of the therapeutic benefit of administering .gamma.-tocopherol and .gamma.-tocopherol derivs. More specifically, the use of .gamma.-tocopherol and racemic LLU-.alpha., (S)-LLU-.alpha., or .gamma.-tocopherol derivs. as **antioxidants** and nitrogen oxide scavengers which treat and prevent high blood pressure, thromboembolic disease, cardiovascular disease, cancer, natriuretic disease, the formation of neuropathol. lesions, and a reduced immune system response are disclosed.

IT **4072-32-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction; .gamma.-tocopherol and **oxidative** metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



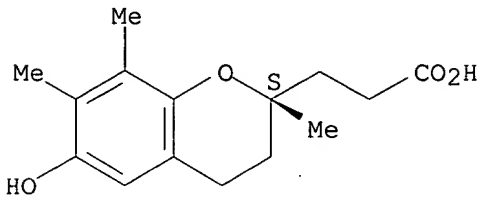
IT **178167-75-4P**
RL: BAC (Biological activity or effector, except adverse); PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(.gamma.-tocopherol and **oxidative** metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-75-4 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl- (9CI) (CA INDEX NAME)



IT **178167-88-9P**
RL: BAC (Biological activity or effector, except adverse); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(.gamma.-tocopherol and **oxidative** metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-88-9 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-,

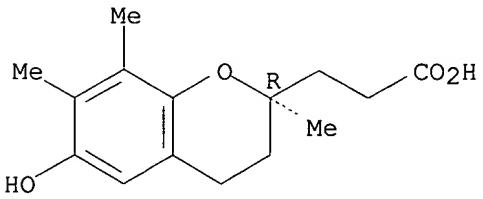
(2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **178167-89-0P**
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(.gamma.-tocopherol and **oxidative** metabolite LLU-.alpha. in treatment of natriuretic disease)
RN 178167-89-0 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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(7) Christen; Proc Natl Acad Sci USA 1997, V94(7), P3217 CAPLUS
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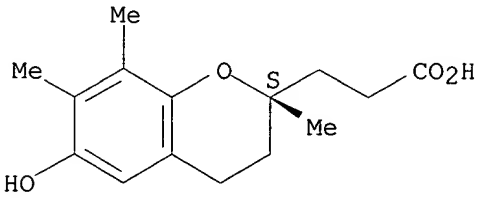
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:530455 CAPLUS
DOCUMENT NUMBER: 127:219945
TITLE: Endogenous natriuretic factors. 6: The stereochemistry of a natriuretic .gamma.-tocopherol metabolite LLU-.alpha.
AUTHOR(S): Kantoci, Darko; Wechter, William J.; Murray, E. David, Jr.; Dewind, Sally A.; Borchardt, Dan; Khan, Saeed I.
CORPORATE SOURCE: Laboratory of Chemical Endocrinology, Loma Linda University School of Medicine, Loma Linda, CA, USA
SOURCE: J. Pharmacol. Exp. Ther. (1997), 282(2), 648-656
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 2,7,8-Trimethyl-(S)-2-(.beta.-carboxyethyl)-6-hydroxy chroman (S-LLU-.alpha.) isolated from human uremic urine is apparently an **oxidative** side-chain degrdn. product of .gamma.-tocopherol. This compd. exhibits natriuretic activity in vivo and it appears to mediate the inhibition of the 70 pS K+ channel in the apical membrane of the thick ascending limb of the nephron. The stereochem. at the C-2 of LLU-.alpha.

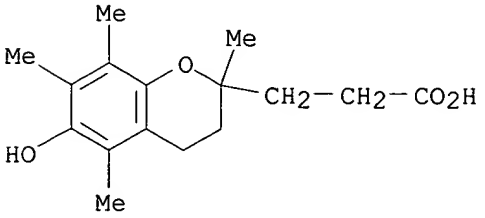
has been unequivocally established to be S(+) by X-ray crystallog. anal. of a diastereomeric amide deriv. It was also established that the chroman ring oxidn. of S-LLU-.alpha. proceeded without racemization at C-2. This finding can be extended to nonepimerization at C-2 of .alpha.-.delta.-tocopherols (Vitamin E) during side-chain oxidn. and stereospecificity (retention or inversion) of **oxidative** opening of the chroman ring. The resoln. of the enantiomers of the parent compd. and derivs. was accomplished by chiral high-performance liq. chromatog. The stereospecific enzymic hydrolysis by an array of com. available enzymes of the racemic Me ester of LLU-.alpha. was investigated. The lipase from Humicola lanuginosa appears to be the best enzyme for resoln. by selective hydrolysis of the racemic Me ester.

IT **178167-88-9P**
RL: BPR (Biological process); MFM (Metabolic formation); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process)
(stereochem. of a natriuretic .gamma.-tocopherol metabolite LLU-.alpha.)
RN 178167-88-9 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,7,8-trimethyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **4072-32-6P**
RL: PRP (Properties); PUR (Purification or recovery); PREP (Preparation)
(stereochem. of a natriuretic .gamma.-tocopherol metabolite LLU-.alpha.)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)

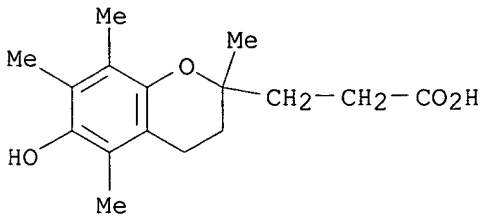


L6 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:265450 CAPLUS
DOCUMENT NUMBER: 126:277465
TITLE: Preparation and formulation of guanidinothiazole derivatives as Maillard reaction inhibitors and **antioxidants**
INVENTOR(S): Matsui, Toshiaki; Tatsumi, Tadashi; Oonada, Shuichi
PATENT ASSIGNEE(S): Ono Pharmaceutical Co, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 53 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent

LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09059258	A2	19970304	JP 1995-225989	19950811

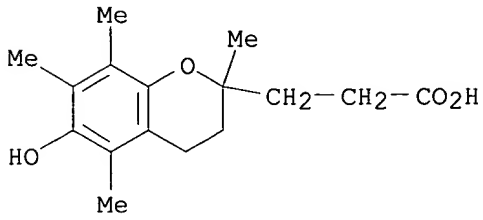
OTHER SOURCE(S): MARPAT 126:277465
GI For diagram(s), see printed CA Issue.
AB The title compds. I [Z = S, etc.; R1 = H, alkyl, etc.; A = bond, alkylene, etc.; ring D is benzoquinone with substituents (generic structure given), etc.] are prepd. The title compd. II.HCl in vitro showed IC50 of 0.82 .mu.M against lipid peroxidn.
IT **4072-32-6**
RL: RCT (Reactant)
(prepn. of guanidinothiazole derivs. as Maillard reaction inhibitors and **antioxidants**)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



L6 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:69202 CAPLUS
DOCUMENT NUMBER: 124:144421
TITLE: Novel urinary metabolite of .alpha.-tocopherol, 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman, as an indicator of an adequate vitamin E supply?
AUTHOR(S): Schultz, Manfred; Leist, Marcel; Petrzika, Marion; Gassmann, Berthold; Brigelius-Flohe, Regina
CORPORATE SOURCE: Department Vitamins and Atherosclerosis, German Institute Human Nutrition, Potsdam-Rehbrucke, D-14558, Germany
SOURCE: Am. J. Clin. Nutr. (1995), 62(6, Suppl.), 1527S-34S
CODEN: AJCNAC; ISSN: 0002-9165
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previously, the metab. of .alpha.-tocopherol was considered to involve the opening of the chroman structure because of its oxidn. to tocopherylquinone. In contrast, we describe here 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman (.alpha.-CEHC) as the major urinary metabolite of .alpha.-tocopherol that appears in human urine after vitamin E supplementation. It is formed directly from .alpha.-tocopherol without previous **oxidative** splitting of the chroman ring. The correlation of .alpha.-tocopherol intake, plasma .alpha.-tocopherol concns., and urinary excretion of .alpha.-CEHC in human volunteers supplemented with RRR-.alpha.-tocopherol dosages ranging from 0 to 800 mg/d was examd. HPLC and gas chromatog.-mass spectroscopy anal. revealed that .alpha.-CEHC was only excreted when a plasma threshold of 7-9 .mu.mol .alpha.-tocopherol/g total lipid was exceeded. This concn. was obtained by a daily intake of .apprxeq.50-150 mg .alpha.-tocopherol. We suggest that .alpha.-CEHC excretion indicates a satd. binding capacity of vitamin

E in the plasma and thus may be considered to be a marker of optimum vitamin E intake.

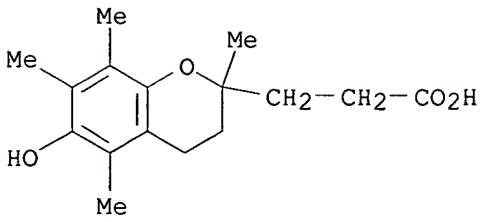
IT **4072-32-6**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(novel urinary metabolite of .alpha.-tocopherol, 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman, as an indicator of an adequate vitamin E supply)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



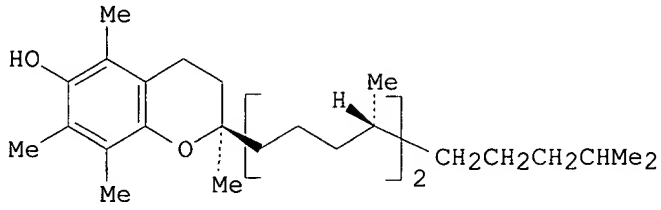
L6 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:45173 CAPLUS
DOCUMENT NUMBER: 120:45173
TITLE: Structure-activity relationship in the quenching reaction of singlet oxygen by tocopherol derivatives and related phenols. Finding of linear correlation between the rates of quenching of singlet oxygen and scavenging of peroxyl and phenoxyl radicals in solution
AUTHOR(S): Mukai, K.; Daifuku, K.; Okabe, K.; Tanigaki, T.; Inoue, K.
CORPORATE SOURCE: Fac. Sci., Ehime Univ., Matsuyama, 790, Japan
SOURCE: Int. Congr. Ser. - Excerpta Med. (1992), 998(Oxygen Radicals), 625-8
CODEN: EXMDA4; ISSN: 0531-5131
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The log of the quenching rates of 1O2 by 15 kinds of tocopherol derivs. and 5 structurally related phenols correlates with their peak oxidn. potentials, Ep. Therefore, the values of kQ have been plotted against k1 and k4, resp. As shown in Figures 2 and 3, the kQ values were found to correlate linearly with the k4 values and the k1 values, resp. The ratios of kQ to k4 and k1 were estd. to be 4.6 x 104 and 56. The result suggests that the relative reactivities, i.e., relative **antioxidant** activities of phenolic **antioxidants** in homogeneous soln. do not depend on whether singlet oxygen, peroxyl radical, and substituted phenoxyl radical is the reactive species. These facts indicate that the property of the transition states in the above singlet oxygen quenching and free radical scavenging reactions by phenolic **antioxidants** is similar to each other, suggesting charge-transfer intermediate.

IT **4072-32-6**
RL: USES (Uses)
(singlet oxygen scavenging by, structure in relation to)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



L6 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:409075 CAPLUS
DOCUMENT NUMBER: 115:9075
TITLE: Structure-activity relationship in the quenching reaction of singlet oxygen by tocopherol (vitamin E) derivatives and related phenols. Finding of linear correlation between the rates of quenching of singlet oxygen and scavenging of peroxyl and phenoxyl radicals in solution
AUTHOR(S): Mukai, Kazuo; Daifuku, Koji; Okabe, Kazuya; Tanigaki, Teiichi; Inoue, Kenzo
CORPORATE SOURCE: Fac. Sci., Ehime Univ., Matsuyama, 790, Japan
SOURCE: J. Org. Chem. (1991), 56(13), 4188-92
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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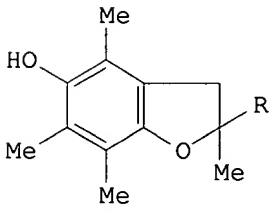

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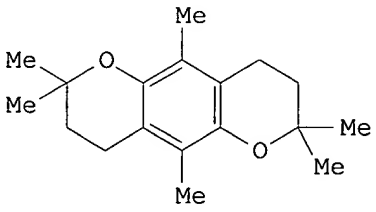
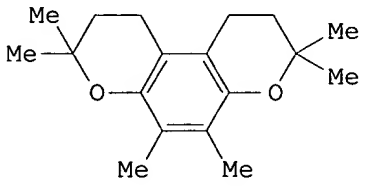


III



IV

AB The rate of quenching of 1O2 by 17 kinds of tocopherol derivs., including .alpha.-(I), .beta.-, .gamma.-, and .delta.-tocopherols, and five structurally related phenols was measured spectrophotometrically in EtOH at 35 .degree.C. The result indicates that the overall rate consts., kQ (kQ = kq + kr, phys. quenching + chem. reaction), increase as the total electron-donating capacity of the alkyl substituents on the arom. ring increases. The log of the rate consts., kQ, was found to correlate with

their half-peak oxidn. potentials, EP/2; the tocopherols that have smaller EP/2 values show higher reactivities. Tocopherols II (R = Me, H) with a five-membered heterocyclic ring were found to be 1.73 and 1.21 times more active than I, resp., which has the highest **antioxidant** activity among natural tocopherols and related phenols. Two benzodipyran derivs. III and IV having no OH group were also found to be 1.63 and 1.33 times more active than I. The quenching rates, kQ, obsd. were found to be related linearly to the rates k1 and k3 of scavenging of peroxyl and phenoxyl radicals by these tocopherols, resp., reported previously by Burton et al. and by Mukai et al., except for the benzodipyran derivs. The result indicates that the relative reactivities, i.e., relative **antioxidant** activities of phenolic **antioxidants** in homogeneous soln., do not depend on how singlet oxygen (1O2), peroxyl radical (LOO.bul.), and substituted phenoxyl radical (PhO.bul.) reacted. Further, the result indicates that the properties of the transition states in the singlet oxygen quenching and free radical scavenging reactions by tocopherol are similar, suggesting a charge-transfer intermediate.

IT **133906-49-7**
RL: RCT (Reactant)
(quenching by, of singlet oxygen)

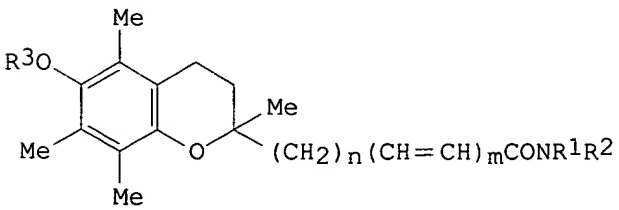
RN 133906-49-7 CAPLUS

L6 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1991:81586 CAPLUS
DOCUMENT NUMBER: 114:81586
TITLE: Preparation of 3,4-dihydro-2H-benzopyrans and their use as pharmaceuticals
INVENTOR(S): Matsuo, Kyoko; Sakane, Soichi; Shiono, Manzo; Yamahara, Joji; Tawara, Tetsuji; Setoguchi, Michihide; Terasawa, Michio
PATENT ASSIGNEE(S): Kuraray Co., Ltd., Japan; Yoshitomi Pharmaceutical Industries, Ltd.
SOURCE: Jpn. Kokai Tokkyo Koho, 17 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 02215778	A2	19900828	JP 1989-35703	19890214

OTHER SOURCE(S): MARPAT 114:81586
GI



I

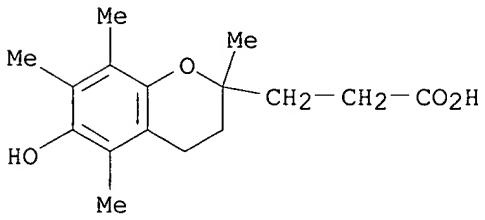
AB Title compds. I [R1 = H, lower alkyl; R2 = H, (un)substituted linear alkyl, aryl, pyridyl; or R1R2 may form (CH2)2O(CH2)2, (CH2)2S(CH2)2, (CH2)2NR4(CH2)2; 2-C6H4SC6H4-2'; R3 = H, protecting group; R4 = H, (un)substituted aryl, aralkyl; m = 0, 1; n = 0-2], which inhibit 5-lipoxygenase, histamine, and lipid peroxidn. and show analgesic effect, are prepd. Pharmaceutical prepns. contain EDs of I (R3 = H; R1, R2, m, n

= same as above) and pharmaceutically acceptable additives. Refluxing 6-benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2H-benzopyran-2-ylacetic acid with SOCl2 in 1,2-dichloroethane contg. DMF mixt. for 2 h, then treatment with 3-aminopyridine at room temp. overnight gave 86.4% I (NR1R2 = 3-pyridyl, R3 = PhCH2, m = 0, n = 1), which was treated with BCl3 in CH2Cl2 at room temp. for 30 min to afford 54.4% I (NR1R2 = 3-pyridyl, R3 = H, m = 0, n = 1) (II). II inhibited 5-lipoxygenase with IC50 of 0.2 .mu.M, vs. 75 .mu.M for caffeic acid.

IT **4072-32-6**
RL: RCT (Reactant)
(amidation of)

RN 4072-32-6 CAPLUS

CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



L6 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1986:497316 CAPLUS

DOCUMENT NUMBER: 105:97316

TITLE: Chroman compounds and their use

INVENTOR(S): Shiono, Manzo; Fujita, Yoshiji; Nishida, Takashi

PATENT ASSIGNEE(S): Kuraray Co., Ltd. , Japan

SOURCE: Eur. Pat. Appl., 46 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

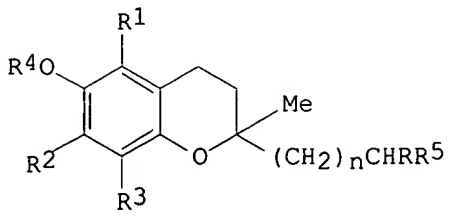
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

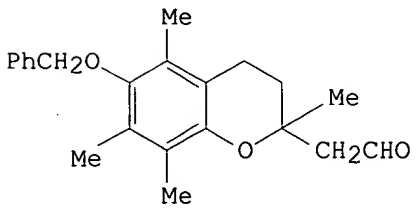
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 183869	A1	19860611	EP 1984-114879	19841206
EP 183869	B1	19910417		
R: CH, DE, FR, GB, IT, LI, NL				
US 4694090	A	19870915	US 1984-679455	19841207
CA 1241009	A1	19880823	CA 1984-469592	19841207

PRIORITY APPLN. INFO.: EP 1984-114879 19841206

GI



I



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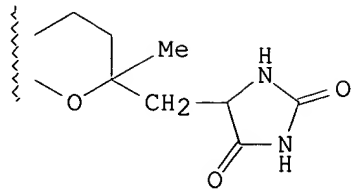
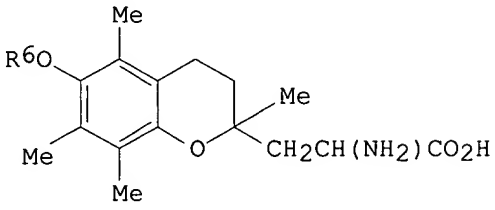


III



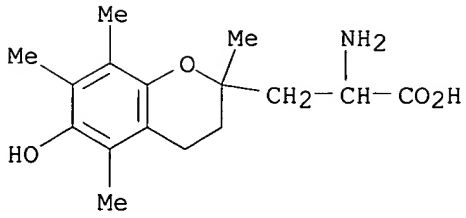
IV

AB Benzopyran derivs. I (R = H, CH2OH, CO2H, R5 = NH2; R = CO2H, R5 = OH; R1 = H, alkyl; R2, R3 = H, alkyl, alkoxy; R2R3 = CH:CHCH:CH; R4 = H, protective group; n = 0-2) and their esters and salts are prepd. (19 examples) as **antioxidants** and analgesics. Thus, benzopyranylacetaldehyde II in aq. EtOH contg. (NH4)2CO3 and NaCN was stirred at 50-55.degree. for 4 h, and the mixt. concd., treated with concd. HCl, heated 5 min at 90.degree., cooled, dild. with H2O, and the ppt. collected to give 83.8% imidazolidinedione deriv. III. Hydrolysis of III with aq. NaOH at 120.degree. (sealed tube) gave 78.7% benzopyranylalanine IV (R6 = PhCH2), which underwent hydrogenolysis over Pd in EtOH contg. HCl to give 61.2% IV.HCl (R6 = H) (V). I were more effective than .alpha.-tocopherol, ascorbic acid, or Na erythorbate in preventing air oxidn. of Na or Et linoleate. At 100 mg/kg s.c. in mice, V gave 96.1% inhibition in the HOAc-induced writhing test, vs. 40.8% for aspirin. I also showed local anesthetic activity, and inhibited isoprenaline-induced bronchodilation. A tablet contained V 100, corn starch 145, Ca carboxymethylcellulose 40, polyvinylpyrrolidone 9, and Mg stearate 6 mg.

IT **103945-99-9**
RL: RCT (Reactant)
(**antioxidant** activity of)

RN 103945-99-9 CAPLUS

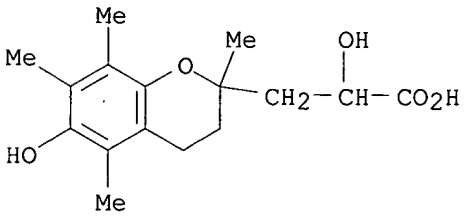
CN 2H-1-Benzopyran-2-propanoic acid, .alpha.-amino-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-, monosodium salt (9CI) (CA INDEX NAME)



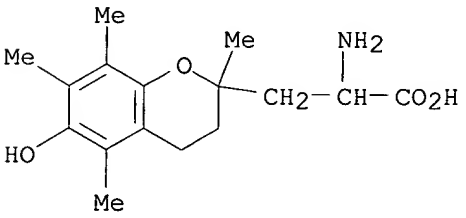
● Na

IT **96909-73-8P 97322-21-9P 97322-27-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as analgesic and **antioxidant**)

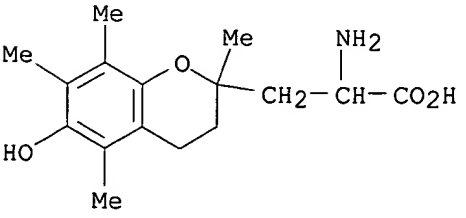
RN 96909-73-8 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-.alpha.,6-dihydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



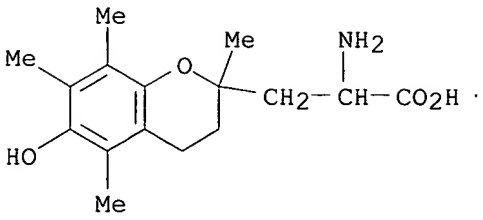
RN 97322-21-9 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, .alpha.-amino-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



RN 97322-27-5 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, .alpha.-amino-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-, hydrochloride (9CI) (CA INDEX NAME)



HCl



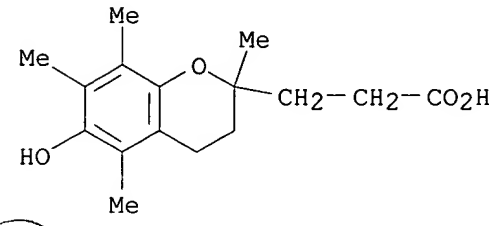
● HCl

L6 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:615586 CAPLUS
DOCUMENT NUMBER: 103:215586
TITLE: **Autoxidation** of biological molecules. 4. Maximizing the **antioxidant** activity of phenols
AUTHOR(S): Burton, G. W.; Doba, T.; Gabe, E.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, Keith U.
CORPORATE SOURCE: Div. Chem., Natl. Res. Counc. Canada, Ottawa, ON, K1A 0R6, Can.
SOURCE: J. Am. Chem. Soc. (1985), 107(24), 7053-65
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 103:215586

AB Rate consts., k1, for H-atom abstraction by peroxyl radicals from .alpha.-tocopherol and 34 structurally related phenols have been measured at 30.degree.C by the inhibited autoxidn. of styrene (IAS) method. An independent laser-flash kinetics EPR method was used with 9 of these phenols which gave k1 values at 24.degree.C that were in satisfactory agreement with the values found by the IAS method. The relative magnitudes of k1 values for phenols that are structurally closely related and have an oxy substituent para to the hydroxyl group can be correlated with the degree of stabilization of the phenoxyl radical. Stabilization depends on two factors: (i) the extent of orbital overlap between the 2p type lone pair on the para O atom and the arom. .pi. electron system and (ii) the electron-donating or withdrawing character of the group bonded to the para oxygen atom. Orbital overlap depends on the dihedral angle, .theta., between the direction of the 2p orbital on the para O and a line perpendicular to the arom. plane which can be estd. from x-ray structures. In the series 4-methoxytetramethylphenol (I), 6-hydroxy-2,2,5,7,8-pentamethylchromene, 6-hydroxy-2,2,5,7,8-pentamethylchroman, and 2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran (II), k1 increases from 3.9 .times. 105, 2.5 .times. 106, 3.8 .times. 106, to 5.7 .times. 106 M-1 s-1, as .theta. decreases from 89, 38, 17, to 6.degree.. Compd. II, the most active **antioxidant**, is 1.8 times more active than .alpha.-tocopherol. For 2-substituted 6-hydroxy-2,5,7,8-tetramethylchromans log (k1/M-1 s-1) can be correlated with the .sigma.I const. of the 2-substituent, .rho.I = 1.25. For these compds. and for some 2,6-dimethylphenols log (k1/M-1 s-1) can also be correlated with the extent of stabilization of the corresponding phenoxyl radicals as measured by the unpaired spin d. at the two ortho Me groups. It is also shown that the perpendicular methoxy group in I is not deactivating relative to an H atom but is, instead, about as activating as an Me group.

IT **4072-32-6**
RL: RCT (Reactant)
(**antioxidant** activity of, in autoxidn. of styrene, kinetics of)
RN 4072-32-6 CAPLUS

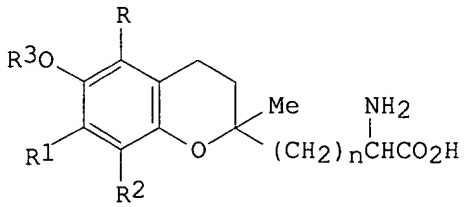
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



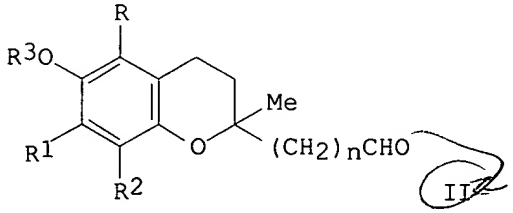
L6 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:453956 CAPLUS
DOCUMENT NUMBER: 103:53956
TITLE: .alpha.-Amino acid derivatives
PATENT ASSIGNEE(S): Kuraray Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 60001177	A2	19850107	JP 1983-108944	19830616
JP 03026191	B4	19910410		

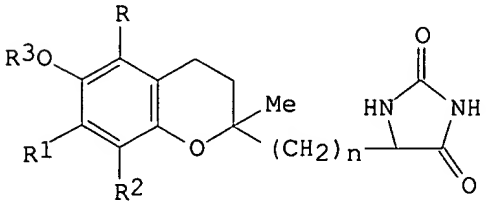
OTHER SOURCE(S): CASREACT 103:53956
GI



I



II



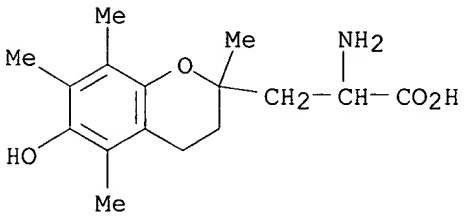
III

AB Eleven .alpha.-amino acid derivs. I (R = H, alkyl; R1, R2 = H, alkyl, alkoxy; R1R2 may be CH:CHCH:CH; R3 = H, protecting groups; n = 0-2) were

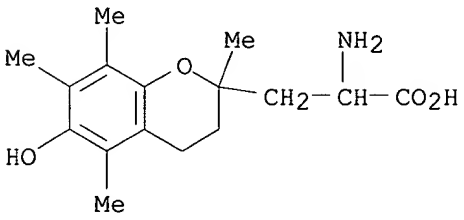
prepd. by reaction of II with (NH4)2CO3 and alkali metal cyanides followed by hydrolysis of the resulting hydantoins (III). Antioxidizing test data of I were shown for linolic acid. Thus, stirring a mixt. of II (R = R1 = R2 = Me, R3 = PhCH2, n = 1) 3.38, (NH4)2CO3 4.52, and NaCN 0.98 g in aq. EtOH 4 h at 50-55.degree. gave 83.8% III (R = R1 = R2 = Me, R3 = PhCH2, n = 1) (IV). Autoclaving 3.15 g IV with 1.6 g NaOH in H2O 15 h at 120.degree. gave 78.7% I (R = R1 = R2 = Me, R3 = PhCH2, n = 1) (V). Stirring 2.3 g V in EtOH contg. 12 mL N HCl and 2 g 5% Pd/C under H current 2 days at room temp. gave 61.2% I.HCl (R = R1 = R2 = Me, R3 = H, n = 1).

IT **97322-21-9P 97322-27-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **antioxidant**)

RN 97322-21-9 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, .alpha.-amino-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



RN 97322-27-5 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, .alpha.-amino-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-, hydrochloride (9CI) (CA INDEX NAME)

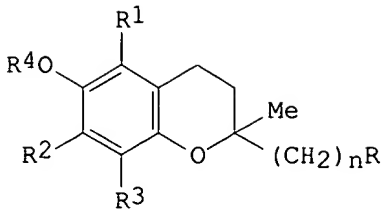


● HCl

L6 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:422462 CAPLUS
DOCUMENT NUMBER: 103:22462
TITLE: .alpha.-Hydroxycarboxylic acids
PATENT ASSIGNEE(S): Kuraray Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 59227877	A2	19841221	JP 1983-103753	19830609
JP 03026190	B4	19910410		

GI



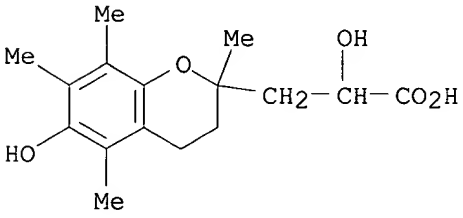
I

AB .alpha.-Hydroxycarboxylic acids I [R = CH(OH)CO2H; R1 = H, alkyl; R2, R3 = H, alkyl, alkoxy; R2R3 may be CH:CHCH:CH; R4 = H, protecting groups; n = 0-2] were prepd. I are useful as anti-**oxidants** for oil, rubber, plastic, and manufd. foods. Thus, 0.34 g NaCN in H2O was added to a mixt. of 1.18 g aldehyde I (R = CHO, R1 = R2 = R3 = Me, R4 = PhCH2, n = 1) and 0.73 g NaHSO3 in aq. EtOH at room temp. to give the corresponding cyanohydrin which was refluxed with 20 mL 36% aq. HCl to give 0.84 g acid I [R = CH(OH)CO2H, R1 = R2 = R3 = Me, R4 = H, n = 1]. Four addnl. I were similarly prepd.

IT **96909-73-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **antioxidant** activity of)

RN 96909-73-8 CAPLUS

CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-.alpha.,6-dihydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



L6 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1978:486100 CAPLUS

DOCUMENT NUMBER: 89:86100

TITLE: **Oxidation** of .alpha.-tocopherol with the superoxide radical (O2-)

AUTHOR(S): Yagi, Kunio; Yamada, Hiroshi; Nishikimi, Morimitsu

CORPORATE SOURCE: Fac. Med., Univ. Nagoya, Nagoya, Japan

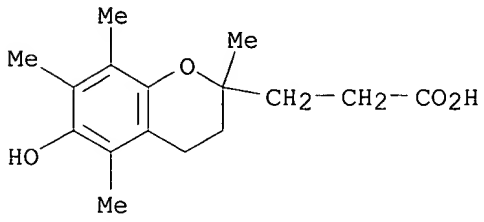
SOURCE: Tocopherol, Oxygen Biomembr., Proc. Int. Symp. (1978), Meeting Date 1977, 1-11. Editor(s): De Duve, Christian; Hayaishi, Osamu. Elsevier: Amsterdam, Neth.
CODEN: 38PDAD

DOCUMENT TYPE: Conference

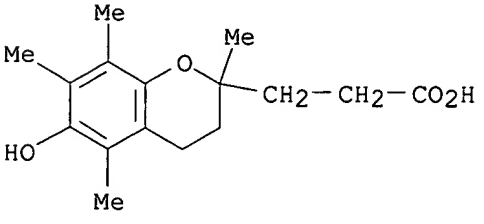
LANGUAGE: English

AB An .alpha.-tocopherol (I) model compd., 3-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)propionic acid (II), was oxidized by the superoxide-generating system xanthine-xanthine **oxidase**. The oxidn. kinetics of II with superoxide were 2nd order with a value of 5.9 .times. 103 M-1 s-1 (pH 7.4, 25.degree.). Na deoxycholate micelles contg. I were also oxidized by superoxide. KO2 reaction with I formed a compd., X, which slowly converted to I or a I-like deriv. X oxidized KI to I in the presence of AcOH.

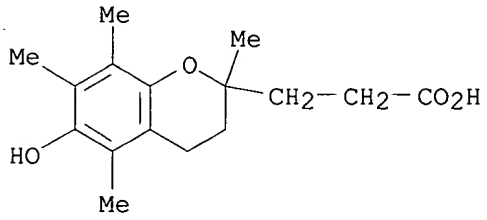
IT **4072-32-6**
RL: RCT (Reactant)
(oxidn. of, by superoxide)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



L6 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1978:472173 CAPLUS
DOCUMENT NUMBER: 89:72173
TITLE: Enhancement of DNA chain breakage by bleomycin and biological free radical producing systems
AUTHOR(S): Yamanaka, Naoki; Fukushima, Masanori; Koizumi, Keiko; Nishida, Keiko; Kato, Taketoshi; Ota, Kazuo
CORPORATE SOURCE: Lab. Chemother., Aichi Cancer Cent. Res. Inst., Nagoya, Japan
SOURCE: Tocopherol, Oxygen Biomembr., Proc. Int. Symp. (1978), Meeting Date 1977, 59-69. Editor(s): De Duve, Christian; Hayaishi, Osamu. Elsevier: Amsterdam, Neth.
CODEN: 38PDAD
DOCUMENT TYPE: Conference
LANGUAGE: English
AB DNA cleavage induction by bleomycin (I) and the stimulation of I-induced cleavage by free radical-forming systems were studied. The NADH-dependent microsomal electron transport system (free radical-forming) increased DNA cleavage by I in isolated mols., nuclei, and in intact cells. 2-Thiobarbiturate-reacting compds., which occurred during I-induced DNA cleavage, were inhibited by hydralazine derivs., but not by **antioxidants**. I-Cu2+ had no effect on DNA but did increase microsomal lipid peroxidn. **Antioxidants** inhibited this peroxidn.
IT **4072-32-6**
RL: BIOL (Biological study)
(lipid peroxidn. by microsome enhancement by bleomycin-copper complex inhibition by)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



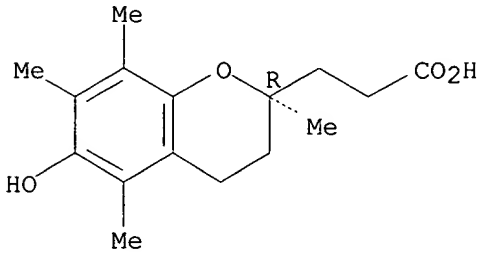
L6 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1976:30811 CAPLUS
DOCUMENT NUMBER: 84:30811
TITLE: Chlorinations of 5-methyl-6-chromanols and reactivities of 5-chloromethyl-1-6-chromanols
AUTHOR(S): Murase, Kiyoshi; Matsumoto, Jun; Tamazawa, Kazuharu; Takahashi, Kozo; Murakami, Masuo
CORPORATE SOURCE: Yamanouchi Cent. Res. Lab., Tokyo, Japan
SOURCE: Yamanouchi Seiyaku Kenkyu Hokoku (1974), 2, 66-73
CODEN: YSKHDO
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
GI For diagram(s), see printed CA Issue.
AB 2,2,5,7,8-Pentamethyl-6-chromanol and its acetate were monochlorinated with SOCl2, SO2Cl2, Cl2 and PCl5 to give 5-chloromethyl-2,2,7,8-tetramethyl-6-chromanol (I) and its acetate (II), resp. I was more reactive than II. 5-Acetoxymethyl-2,2,7,8-tetramethyl-6-chromanyl acetate was prepd. by heating I with AgOAc in AcOH. I was treated with silica gel in petroleum ether to give III, which was also prepd. from I in ether in the presence of H2O and ClCH2CO2H or 80% H3PO4. I readily reacted with phenols. Thus, I and p-cresol gave 2,2,7,8-tetramethyl-5-(2-hydroxy-5-methylbenzyl)-6-chromanol (IV). These reactions were applied to .alpha.-tocopherol analogs. III and IV showed **antioxidant** activity.
IT **4072-32-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and acetylation of)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



L6 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1974:449523 CAPLUS
DOCUMENT NUMBER: 81:49523
TITLE: 6-Hydroxychroman-2-carboxylic acids. Novel **antioxidants**
AUTHOR(S): Scott, John W.; Harley, Hampton; Cort, Winifred M.; Parrish, David R.; Saucy, Gabriel
CORPORATE SOURCE: Hoffmann-La Roche Inc., Nutley, N. J., USA
SOURCE: J. Amer. Oil Chem. Soc. (1974), 51(5), 200-3
CODEN: JAOCA7
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 6-Hydroxychroman-2-carboxylic acids (I) are effective **antioxidants** in animal fats, vegetable oils, and emulsion systems. Two new syntheses of I were developed. Structure-activity correlations for I with various substituents at C2, C5, C7, and C8 in various test systems were obtained. The homol-ogous chromanacetic acids, which are also **antioxidants**, and some other derived compds. were also synthesized. The most effective **antioxidant** in this series was 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid. This compd. has activity which compares well with the better commercial **antioxidants**.

IT **53152-73-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 53152-73-1 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1969:2500 CAPLUS
DOCUMENT NUMBER: 70:2500
TITLE: **Antioxidative** effect of various polymethylhydroxychroman derivatives and of (+-)-.alpha.-tocopherol
AUTHOR(S): Placer, Z.; Weichet, J.
CORPORATE SOURCE: Inst. Ernaehrungsforsch., Prague, Czech.
SOURCE: Nahrung (1968), 12(4), 491-2
CODEN: NAHRAR
DOCUMENT TYPE: Journal
LANGUAGE: German
AB The **antioxidative** effects of 5,7,8-trimethyl-6-, 2,5,7,8-tetramethyl-6-, 2,2,5,7,8-pentamethyl-6-,2,5,7,8-tetramethyl-2-carboxyethyl-6-hydroxychroman, butylated hydroxytoluene, and Pr gallate in both Hb-activated emulsions of .gamma.-linolenic acid in rat liver homogenates were significantly greater than that effect exerted by (.+-.)-.alpha.-tocopherol.
IT **4072-32-6**
RL: BIOL (Biological study)
(as **antioxidant**)
RN 4072-32-6 CAPLUS
CN 2H-1-Benzopyran-2-propanoic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)